HYPOPHYSECTOMY

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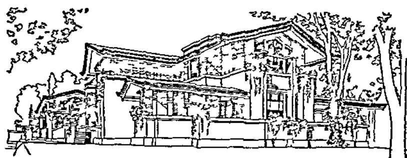
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FOREWORD

INTEREST in the effects of the endocrine environment on the growth of human neoplasms has grown steadily during the past fifteen years The possibility that the pituitary gland might play an important role in the growth of certain neoplasms has been speculated upon for some time Although sporadic attempts had been made to remove the hypophysis in man it was not until cortisone became available and was found to be effective replacement therapy in adrenal insufficiency that hypophysectomy seemed to be a reasonable procedure to undertake Attempts to perform hypophysectomy in man began independently in several clinics almost simultaneously

Dr C P Rhoads Director of the Sloan Kettering Institute Memorial Center suggested that a conference of workers interested in this field might be helpful in evaluating the potential of hypophysectomy The meetings were held on March 19 and 20 1956 at the Sloan Kettering Institute in New York The conference was made possible by generous support from the Alfred P Sloan Foundation All of the contributors to the symposium felt that the sharing of their experiences had been very useful and that publication of the proceedings should prove helpful to others who might become interested in the effects of removal of the pituitary gland

Sincere appreciation is due Mrs Helena Curtis for assistance in editing the discussions

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CONTENTS

HYPOPHYSECTOMY

I

SURGICAL HYPOPHYSECTOMY IN PATIENTS WITH CANCER

DR. ROLF LUFT

IN a recent report [1] we described our results in patients with metastatic breast cancer hypophysectomized be fore June 1954 The main part of this report will deal with the continued course of this first group of patients In the small series treated since that date however the propor tion of favorable responses has been on the whole of the same magnitude Experience with this latter group also has confirmed previous evidence that three types of pa tients are not improved by hypophysectomy 1) patients above an approximate age limit of sixty years 2) patients with metastases to the central nervous system and 3) patients with liver enlargement due to metastases

Summary of Cases

To recapitulate our first series included thirty seven unselected cases of breast cancer nearly all with wide spread metastases (see Tables 1 and 2) In four patients the hypophysectomy was known to be far from complete and three patients died of other causes shortly after the operation Seven of the remaining thirty patients be longed to one of the previously mentioned unfavorable groups Thus there remained twenty three patients who could be evaluated of whom fourteen were alive in June 1954 Of the nine who died three had shown consider able improvement for some time Up to March 1 1956

I

CER OF THE BREAST SUBMITTED TO HYPOPHYSECTOMY

Case no. Sex	Met stases				C d tl f p tient t hypophysectomy				
	Discovered	Locatlo	Treatment: Date	Treatment: Type	G co d	Wt los	P l	F	Dy p ea
1 F	1948 1949	Skin, local. Right breast	1948	Irrad C trati TP P^{32}	F i	+	–	–	+
2 F	1949 1950 1951	Left axilla. kin, local. Bo	1949 1950 1951 52 1951	Irrad Irr d Est ogens. Irrad	F l	–	+	–	–
3 F	1950 1951	Region, odes. kin, local	1950-52 1948 52	Irrad. TP	Poo	+	+++	–	++
4 F	1950 1951 1952	Pain, hip. P in, leg Brai	1952 1952	Irrad TP	Poo	+	+++	–	+
5 F	1952 1952	Regio nodes. Ce bell m	1952	Remo brai met s.	Good	–	–	–	–
6 F	1950 1952	Region, nodes. Bon			F ir	?	+++	–	–
7 F	1952 1952 1952	Skin, local. Regio nodes. Cer bell m	1952	R mov brai metas.	Good	–	–	–	–
8 F	1951 1951 1952 1952 1952	Region, nodes. Co tralat. nod s. Bon kin, local. Left pleura	1952	I rad.	F i	+	+	+	+
9 F	1948 1951	Region, nodes. Bone	1951 5	TP	F i	–	++	–	
10 F	1950 1951	Region, odes. B ne	1951 52 1952	Irrad TP	F ir	+	++	–	–
11 F	1950 1952 1952 1952 53	Region, odes. Right breast. Right axilla. Skin, local	1952 53 1952 53 1952	Irr d TP R mov rt b st+ ill	Good	+	+	–	–
12 F	1950 1952 1952	R gion, nodes. Co tralat. od s. Bone	1952 1952 1953	Right axilla. Irr d TP	Poo	+	++	–	–
13 M	1947 1951 1952	Region, odes. Lu gs Left supracla	1947 1951 53 1952 1952	R m lt. illa. P iph non. Estr g s. Irrad	Good	+	–	–	+
14 F	1950 1953	Brain Bon	1951 1951 1952 1953	Rem brain m t s. Irrad. TP R mov m t s. sk ll	Good	–	++	–	–
15 F	1950 1952	Region, odes. Eyes	—	——	F ir	+	++	+	+
16 F	1951 1951	R gion, nod s. kin, local	1951 53	Irrad	Poo	+	+	+	–
17 F	1950 1953 1953	Region, odes Sk n, local. Bon	—	——	Good	–	+	–	–
18 F	1952	Bone	1952 1953	Irr d TP	F i	+	+	–	–
19 F	1951 1952 1953	Region, odes. Bo Brain	1953	I rad	F l	+	+	–	–
20 F	1949 1951 1952 1953	Region, odes. Lef supracl kin, local. Bone	1949-52 1953	T l radl m TP	F ir	–	+	–	–
21 F	1951 1953	Bone Lu gs	—	——	Fair	+	+	–	+
22 F	1951 1952	Region odes. Bo	1953	TP	Poor	+	+++	+	–
23 F	1952 1953	Region, nodes. Skin, local	1953 1953 1953	Cast tion. Irrad. TP	Good	–	+	–	–
24 F	1950 1951	R gion, nodes. Regi n, nodes.	1953	Irrad.	F ir	–	–	–	–
25 F	1953 1953	Right supracl Lungs	1953	Irrad	Fair	–	++	–	+
26 M	1951 1952	Left sup acla Lungs	1951	Irrad	F ir	+	–	–	+
27 F	1949 1952	Region, nodes. Bon	—	——	Fai	+	+++	–	–
28 F	1947 1953	Region, nodes. Bone	—	——	Fair	+	+++	–	–
29 F	1951 1952 1954	Region, nodes. Bone Lungs	1953	Irrad.	Good	–	+	–	–
30 F	1950 1952	Region, nodes. Bone	—		Poor	+	+++	+	–

TABLE

CLINICAL DATA IN THIRTY CASES OF METASTATIC CAN

Born	Amenorrhea sin e	Breast cancer oted	B east	B ea t per yr	Axill ry node resect.	Other t eatment	Type of cancer
1902	1948	1945	Left	1945	+	Irrad.	Scirrhous
1891	1940	1946	Left	1947	–	Irrad	Poor d.ff solid
1906	1951	1948 pains 1950 lymph node. 1951 breast	Left	—	–	Irrad	Poor diff solid
1909	Regul r m str	1950	Right	1950	+	I rad	Poor d ff solid
1909	Regular menstr	4/1952	Left	4/1952	+	Irrad	Solid
1903	1951	1950	Left	1950	+	Irrad.	Poor diff.
1904	1951	3/1952	Right	—	–	Irrad.	Unknown
1916	Regular menst	1951	Left	1951	+	Irrad	Poor diff & a noca.
1888	1943	1948	Left	1948	+	Irrad. tele-rad um	Solid adenomatous
1877	1924	1950	R ght	1950	+	Irrad.	Simplex
1913	Regular m nstr	1950	Left	1951	+	Irrad	Poo d ff solid
1894	1944	1950	Left	1950	+	Irrad	Solid denomatous
1888		1945	Left	1945	–	Irrad.	Unknown
1914	1952	1951	Left	1951	+	Irrad.	Adenoca.
1902	1952	1950	Right	1953	+	Irrad. TP	Scirrhou
1896	1945	1951	Left	—	–	See metas.	Poor diff
1899	1948	1948	Left	1950	+	Irrad	Poor diff
1903	1948	1947	Left	1948	+	Irrad.	Solid d nom tous
1905	Regular menstr	1951	Left	1951	+	Irrad.	Solid tubular
1909	1949	1949	Left	1949	+	Irrad. castration	Solid adenom tous
1905	Irreg. menstr	1949	Left	1951	+	Irrad.	Scirrhous
1898	1948	1951	Right	1951	+	Irrad.	Poor diff (scirrhous)
1910	Regular menstr	1952	Right	1952	+	Irrad.	Poor diff solid
1855	1938	1950 1951	Left Right	1950 1951	+ +	Irrad.	Poor diff solid
1901	Regular menst	1951	Right	1951	+	Irrad.	Solid scirrhous
1894		1948	Left	1948	+	Irrad.	Adenoca. Poor diff
1908	Regular menstr	1948	Left	1949	+	Irrad.	Poor d.ff
1910	Regula menstr	1947	Left	1947	+	Irrad.	Solid tubular
1921	2/1953	1951	Right	1951	+	Irrad.	Poor diff (adenoca.)
1906	Irreg. menstr	1950	Right	1950	+	Irrad.	Poor diff

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the cerebellum At autopsy no other metastases could be demonstrated

Case 11 The patient was asymptomatic for thirteen months postoperatively She died twenty six months after the operation Autopsy revealed extensive involvement of the liver

Case 13 (Male) This patient was well and active up to the time of our examination eighteen months after hypophysectomy While in the hospital for study he acquired without known trauma, a compression of one of the thoracic vertebrae which has since kept him in bed with considerable pain He was alive thirty five months after hypophysectomy

Case 15 New metastases appeared fifteen months after hypophysectomy pain recurred three months later and the patient expired twenty two months postoperatively

Case 16 After the hypophysectomy a small ulceration and infiltration of the skin above the remaining primary tumor persisted This remained unchanged for twenty three months postoperatively after which the infiltration and ulceration increased slowly The patient died thirty three months after the operation of septicemia No distant metastases could be revealed at autopsy

Case 17 The patient was alive and asymptomatic thirty four months after hypophysectomy

Case 21 For thirty months after hypophysectomy the patient was asymptomatic From then on moderate epi gastric distress and slow enlargement of the liver were observed She died thirty three months after hypophysec tomy with extensive metastases involving the liver

Case 25 The patient showed some improvement for eight months after the operation We have been told that she died nine months postoperatively The patient was a drug addict, and it is difficult to get reliable information about her

Case 26 The patient was asymptomatic twenty eight months after hypophysectomy

the following could be stated about the fourteen patients (the numbering of the cases refers to Tables 1 and 2)

Case 1 The patient was asymptomatic for nineteen months following hypophysectomy then progression of soft tissue metastases was noted She was still alive fifty months post hypophysectomy

Case 5 Before the hypophysectomy the only metastasis found was a solitary one in the cerebellum which was extirpated The patient died twenty three months post operatively after the extirpation of a local recurrence in

TABLE 2

EXTENT OF METASTASES AND POSTOPERATIVE OBSERVATION TIME IN THIRTY CASES OF METASTATIC CANCER OF THE BREAST SUBMITTED TO HYPOPHYSECTOMY

Case no	Age at operation yr	Months observation post operative	Metastases: Local	Skeleton	Lungs pleurae	Eyes	Bra n	Liver	Status
1	50	28	++++		+				Living
5	43	20					+		Living
11	40	14	++	++					Living
13	65	14	+		++++				Living
15	51	13		+++	+++	++			Living
16	57	13	+++						Living
17	54	13	+	+					Living
21	48	12	+	++					Living
25	52	7	+		+++				Living
26	57	7	+	++	++				Living
27	45	7	+	++++					Living
28	43	6		++					Living
29	32	3		+++	++				Living
30	46	19	+	+++					Living
2	61	17	++	++					Dead
3	46	1	++++	+	++			+	Dead
4	43	2		+++	++++		+	+	Dead
6	50	3		++	++			+	Dead
7	48	10	+++				+		Dead
8	46	9	++++	+++	+				Dead
9	65	5	+	++	?+				Dead
10	76	10	+	++++					Dead
12	59	10	+	++++					Dead
14	39	4		+			+		Dead
18	50	9	+	++++					Dead
19	48	2		++	++		+		Dead
20	44	2	++++	+	+	+		?+	Dead
22	55	3		+++	+				Dead
23	43	3	++++		?+				Dead
24	68	3	++++	+	+				Dead

*The extent of the metastases locally and to the skeleton and lungs is denoted from + to ++++ Metastases to one eye is denoted + to both eyes ++ Metastases to the bra n are denoted + irrespective of their extent. In all cases the l ver metastases denoted + were very exten ve and made the liver palpable before the operation.

plete elimination of the hypophysis was achieved only in a few cases and that in 30 to 40 per cent at the most the pituitary remnants contained not more than single cell layers The remaining 60 to 70 per cent demonstrated more than a single layer of pituitary cells Only a small number had a large pituitary remnant most of these were cases in which there were complications and the operation could not be completed in the usual way

Tonnis *et al*[2] state that remnants of the pituitary anlage in the pharyngeal roof may regenerate after destruction of the hypophysis in humans We have not checked our material in this respect nor have we looked for pituitary remnants along the central part of the pituitary stalk

The Functionally Complete Hypophysectomy All this brings up another question does a hypophysectomy have to be anatomically complete in order to bring about a favorable effect or can we be content with a hypophysectomy that is complete from a functional point of view? Furthermore what are the possibilities of defining a functional hypophysectomy? During the past four years we have exerted efforts to find the laboratory test or tests that give the best information about the "degree of hypophysectomy The difficulties of solving this problem may be seen from the following review which is based on results obtained during the last two years All the following laboratory studies were performed at least six weeks after operation According to our experience laboratory tests performed during the first six postoperative weeks have a very limited practical value

Laboratory Findings

Almost none of the patients showed the ability postoperatively to respond normally to subcutaneous administration of ACTH or epinephrine A normal response was

Case 27 The patient was asymptomatic twenty seven months after hypophysectomy

Case 28 The patient was asymptomatic for twenty five months after hypophysectomy and was alive twenty six months after the operation but slight pain has re appeared

Case 29 The patient was asymptomatic for fifteen months after hypophysectomy Then there was sudden progression of disease and she died eighteen months postoperatively

Case 30 The patient was asymptomatic for fifteen months then pain reappeared and simultaneously the liver became palpable She expired twenty three months after hypophysectomy with extensive metastatic involve ment of the liver

As to the objective findings on palpation and x ray examination of lungs and skeleton, we have found that in general the improvement obtained during the first year after hypophysectomy has remained constant during the asymptomatic period Further regression of the metastases has not been noted

Completeness of Hypophysectomy

Next I would like to discuss some questions of impor tance in connection with this procedure

The Anatomically Complete Hypophysectomy The first concerns completeness of the hypophysectomy A complete hypophysectomy from an anatomical point of view, can be defined only in one way serial sectioning of the content of the sella turcica shows that no pituitary tissue is left In this respect I can give only preliminary data from twenty-six cases studied This material includes even those cases in which we could presume that the hypophysectomy was incomplete We estimate that com

Our work with all these and other tests of endocrine function has made clear to us the difficulty of estimating whether or not pituitary function has disappeared completely I leave the question open as to whether or not the thyroid gland the gonads, and the adrenal cortex of humans have an autonomous basal function after hypophysectomy

I would like to mention the following in four patients we studied the effect of an intravenous infusion of ACTH on the excretion of 17 ketosteroids and 17 ketogenic steroids In all four the steriod excretion increased due to the stimulation of the adrenal cortex The condition of three of these patients all of whom had shown promising improvement up to the time of the control examinations deteriorated within one month after the studies This change for the worse could not be arrested and the patients died within a few months

Correlation of Laboratory and Clinical Findings

We have not as yet examined our material as regards 1) the correlation between the tests of endocrine functions and the therapeutic effect and 2) the correlation between these tests and the results of the histological examination of the sella turcica and of the peripheral endocrine glands Among the patients who responded favorably however are some whose thyroid function was unimpaired according to the radioiodine tests For example

Case 16 This woman born in 1896 was hypophysectomized in April 1953 The latest control study in November 1955 showed the following BMR −29 per cent thyroid clearance 20 ml per minute 24 hour uptake of I 131 30 per cent conversion rate in twenty four hours 8 per cent and in forty eight hours 46 per cent ACTH test negative calcium in urine 20 mg per day 17 keto

defined as a decrease in the number of circulating eosinophils by at least 40 per cent If the patients were on cortisone the epinephrine test was usually positive

The excretion of *17 ketosteroids* and *17 ketogenic steroids* (according to Norymberski[3]) was one to two mg in at least 75 per cent of tests performed on patients who were not receiving substitution therapy but was completely absent only in a few tests When cortisone was given in a dose of 25 mg daily, the excretion of 17 ketosteroids increased by 1 to 3 mg Our experience with the steroid excretion during administration of prednisone or similar preparations is very limited

As to thyroid function, the BMR decreased in all cases, usually to about -20 per cent to -30 per cent We have used the following criteria for complete or almost complete depression of thyroid function

Thyroid clearance of I 131	<3 ml /min
24 Hour uptake of I 131	<8%
Conversion rate of I 131 in 24 hours	<2%
Conversion rate of I 131 in 48 hours	<2%
Protein bound I 131 in % of dose given	<0 1%
PBI (at least 2 months after operation)	<2 5 µg/%

Sixteen out of twenty nine patients examined, or 55 per cent fulfilled these requirements of a complete or almost complete depression of thyroid function

The capacity to concentrate the urine to a specific gravity above 1 010 was restored in practically all cases after five to six months Recent examinations have shown that antidiuretic hormone can be produced after hypophysectomy

The capacity to increase the secretion of adrenalin during insulin hypoglycemia was intact after hypophysectomy

The excretion of calcium in the urine decreased markedly in most of the cases

sectomy to patients with metastatic breast cancer and patients with diabetes mellitus with vascular complica tions We also have performed the operation in one case of Cushing s syndrome with recurrence after subtotal adren alectomy This patient is still in complete remission six months after the operation You may also remember that almost five years ago we electrocoagulated the hypophysis of a patient with a very advanced Cushing s syndrome This patient is still in remission menstruates regularly and has even become pregnant

We have not continued our trials to influence prostatic cancer and malignant melanomas by hypophysectomy

We cannot elucidate the important question of whether or not hypophysectomy has any therapeutic effect be-yond that achieved by hormone treatment and bilateral adrenalectomy and oophorectomy We have performed hypophysectomy in four patients previously treated by adrenalectomy and oophorectomy All of the patients were of the types previously described as not being im proved by hypophysectomy

steroids, 2 8 mg per day (while on 25 mg of cortisone per day) The patient never needed thyroid substitution Despite the obviously normal thyroid function the patient showed no progression of disease for twenty four months after hypophysectomy At autopsy the thyroid gland was found to be of normal size the adrenals however showed marked atrophic changes

Case 28 This woman born in 1910 was hypophysectomized in December 1953 The last control study in the fall of 1955 showed BMR −20 per cent thyroid clearance 19 ml per minute 24 hour uptake of I 131 50 per cent PBI 1 8 gamma per cent ACTH test positive excretion of 17 ketosteroids 3 4 mg per day (while on 25 mg of cortisone per day) calcium in urine 150 mg per day There was no thyroid substitution Despite the obvious incompleteness of the hypophysectomy the patient was asymptomatic for twenty six months after the operation

Thus it seems that a complete hypophysectomy may not be a prerequisite for a favorable response But despite this finding in a few cases we continue to demand a complete hypophysectomy so as to be able to evaluate correctly the therapeutic value of the procedure

In order to achieve complete hypophysectomy, we have modified our earlier method of surgical removal of the gland the mechanical evacuation has been made more effective and the dura linings of the sella have been cauterized both with 1N NaOH and Zenker s fluid in doing this we have not been able to avoid some damage to the right optic nerve In two cases we tried to destroy the hypophysis by injecting 10 mc of radioactive chromic phosphate into the intact gland however we were not able to make the solution remain in the sella and are therefore unable to evaluate this method

On the whole we have limited the use of hypophy

Morbidity The important complications after operation are listed in Table 4 Each of the two patients with "im portant visual loss retained some degree of useful vision and in the five with minor visual loss the defects consisted

TABLE 4

Important visual loss	2 patients
Minor visual loss	5 patients
Neurological complications	3 patients
Intracranial clots	2 patients
Impaired olfaction (estimated)	40%

of quadrantic temporal impairment which was either un noticed or unimportant to the patient It is believed that although visual impairment was usually the result of acci dental trauma or excessive handling of the optic nerves

TABLE 5

Criteria for Evaluating Remission

Arrest (8 Cases)
No progress of previous lesions
Disappearance of hypercalcemia and hypercalcuria
Improvement in myelophthisic anemia
Regression (28 Cases)
Recalcification of bone lesions
Diminution in size of any lesion
No new lesions
No progression of old lesions

there is a possibility that in some cases minute nutrient blood vessels to the nerves may have been damaged in the process of freeing the arachnoid from the nerves and pituitary stalk

The neurological complications seen in three patients included transient aphasia and hemiparesis The two pa

as a means of preventing bleeding when it is sectioned and also to insure destruction of any anterior lobe cells that might extend into the stalk In more recent cases the stalk has been divided at the diaphragm sella without coagulation and the incidence of diabetes insipidus requiring pitressin has been significantly reduced

Thyroid replacement is usually not instituted until four to eight weeks after operation since myxedema does not appear before that time Two grains of dessiccated thyroid daily adequately control the myxedema

Clinical Results

In the period between March 1954 and January 1 1955 seventy five hypophysectomies were performed on seventy four female patients with advanced metastatic mammary cancer using the present surgical technique as previously described The data that follow present our experience with this series of patients

It is believed that hypophysectomy was not complete in five cases but in one of these the destruction of the gland was completed by a second operation

Mortality There were seven deaths in the first thirty days following operation making an operative mortality of 9 per cent However the deaths that can fairly be attributed to complications of the operation are more nearly 5 per cent (Table 3)

TABLE 3

Postoperative Deaths in the First Thirty Days

Directly due to surgery	3
Pulmonary embolism at home	1
Advance of metastatic disease unimproved by hypophysectomy	3
TOTAL	7

Case 3 A 34 year old (premenopausal) woman had a radical mastectomy eight months prior to the development of extensive pulmonary and several skin metastases Comparison of a roentgenogram of the chest four months after operation with a preoperative film shows the regression of intrathoracic tumor This patient is teaching school and is still in remission one year after hypophysectomy

Case 4 A 40-year old woman had developed intrathoracic metastases three years following radical mastectomy for carcinoma She then had an oophorectomy followed by dramatic regression of the disease The remission ended after seven months Several months later at the time of hypophysectomy she had extensive neoplastic infiltration of both lungs pleural effusion on one side and bloody pericardial effusion with accompanying enlargement of the cardiac shadow on x ray

Roentgenograms taken only six weeks after hypophysectomy show apparent disappearance of intrapulmonary lesions absence of pleural fluid and diminution in the size of the cardiac shadow Her remission continues ten months after hypophysectomy

Case 5 A 44 year old woman two years after radical mastectomy had extensive skeletal metastases with hypercalciuria and hypercalcemia Comparison of roentgenograms of the pelvis and femur before operation with those taken six months after hypophysectomy shows improved structural appearance

A lantern slide shows the subsidence of hypercalciuria and hypercalcemia within ten days after operation and a concomitant disappearance of azotemia (return to normal from a preoperative BUN of 45 mg per cent)

Summary of Clinical Data

Of the sixty seven patients who survived operation six were premenopausal thirty four were postmenopausal sixteen had been oophorectomized and eleven had had

tients with intracranial clots required secondary operations

Impairment of the sense of smell has seemed to be an unavoidable result of deliberate section of the right olfactory nerve and the stretching of the left nerve which occurs when the frontal lobes are displaced by retraction and drainage of spinal fluid Fortunately this is not to be regarded as a serious complication

Remissions Thirty six patients (about one-half) had objective remission of their disease, and of these eight were regarded as having arrest of disease while twenty eight had regression Table 5 lists the criteria employed for determining objective remission of disease Although some patients demonstrated symptomatic improvement they were not counted as remissions unless some objective evidence existed

Examples of Objective Remission

Case 1 A 42 year old (premenopausal) woman presented herself with an ulcerating tumor of the right breast The lesion was raised had a granular and necrotic surface and measured 4 cm in diameter

A photograph six months after hypophysectomy shows marked contraction of the lesion with epithelialization of the surface The patient is still in remission eleven months after operation

Case 2 A woman of seventy two had extensive involvement of the left breast by carcinoma with wide spread of the tumor to adjacent regions of the left chest axilla arm supraclavicular region and even to the right side of the chest wall

A photograph taken nine months after hypophysectomy shows disappearance of the lesion Shortly after this small local recurrences of tumor growth appeared but they have grown very slowly and the patient is otherwise well twenty months after hypophysectomy

tients could not be determined only two of these obtained remission from hypophysectomy

Table 8 shows the results of hypophysectomy in eleven patients previously treated by oophorectomy and adrenalectomy It is notable that hypophysectomy can add to the

TABLE 8

Hypophysectomy in Eleven Cases with Previous Therapeutic Castration and Adrenalectomy

Failure	7
Arrest of disease (Lasting 2, 2, and 3 months)	3
Regression of disease (Lasting 7 months)	1

beneficial effects of the other glandular ablations It is speculative whether this additional effect can be explained on the basis of removal of ACTH effect on accessory adrenal glands or whether in some patients there are other factors such as removal of the source of somatotropic hormone We believe we have some evidence in support of the latter possibility which will be presented hereafter

TABLE 9

Hypophysectomy in Thirty four Postmenopausal Cases

Failure	13
Arrest of disease	2
Regression of disease	19
Average duration of remission	7+ months
Still in remission	10 patients

Table 9 shows the results of hypophysectomy in thirty four postmenopausal patients Some of the patients had undergone a natural menopause while others had undergone artificial menopause prior to the development of

both oophorectomy and adrenalectomy performed prior to hypophysectomy Though the numbers are relatively small some inferences and tentative conclusions can be deducted

Table 6 shows results of primary hypophysectomy in six

TABLE 6

Premenopausal Hypophysectomy in Six Cases

Failure	3
Arrest of disease 2 months (Patient died of brain damage from irradiation)	1
Regression of disease (lasting 7 and 11+ months)	2

premenopausal women none of whom had received hormonal therapy Three patients showed objective remission of their disease

Table 7 shows the results of hypophysectomy in sixteen patients previously treated by oophorectomy The table

TABLE 7

Hypophysectomy in Sixteen Cases with Previous Oophorectomy

Failure		8
Arrest of disease		2
Regression of disease		5
Not evaluated		1
Response to castration	5	5 Response to hypophysectomy
No response to castration	4	1 Response to hypophysectomy
Unevaluated castration	7	2 Response to hypophysectomy

shows that of the five patients known to have had a temporary remission following oophorectomy all obtained a new remission from hypophysectomy Of four patients who failed to improve as a result of oophorectomy one obtained a remission from hypophysectomy The effects of previous oophorectomy on the remaining seven pa

This table shows that the average survival period of the thirty-one patients who were not benefited by hypophysectomy was 4 4 months and that only seven of the thirty one are still living The figures give mute evidence of the advanced stage of disease existing in the majority of the patients who have been operated on There is nothing to indicate that hypophysectomy if it is not beneficial accelerates the disease

The average survival period of the patients who obtained objective remission thus far is twice as long as the average of patients who did not respond to hypophysectomy and twenty one of the thirty six patients are still living

Summary and Conclusions

The results of seventy five hypophysectomies in seventy four women with advancing mammary carcinoma who were operated on between March 1954 and January 1 1956 are reviewed

There were seven deaths in the first thirty days after operation with three deaths directly attributable to the operation

Of the sixty seven patients who survived operation thirty six had objective remissions of their disease and thirty one were not benefited

New remissions can be obtained by hypophysectomy in patients who have been temporarily benefited by oophorectomy or by a combination of oophorectomy and adrenalectomy Every patient that was temporarily benefited by oophorectomy obtained a new remission after hypophysectomy and four of eleven patients having had adrenalectomy obtained a new remission from hypophysectomy

It is suggested that if hypophysectomy is not employed

breast carcinoma The effects of hypophysectomy were the same in the two groups On the whole, the results are better than in any other group of cases with 62 per cent demonstrating remissions following hypophysectomy

TABLE 10

Influence of Endocrine Status on Results of Hypophysectomy in Sixty seven Patients Who Survived Operation

	Cases	*Remissions*
Premenopausal	6	3
Postmenopausal	34	21
Spontaneous	(22)	(14)
Induced non therapeutic	(12)	(7)
Previous therapeutic oophorectomy	16	8
Previous therapeutic oophorectomy and adrenalectomy	11	4

Table 10 shows in summary the influence of the endocrine status on the results of hypophysectomy

Now that a satisfactory technique of operation has been developed it is of importance to determine whether or not hypophysectomy prolongs life It has been demon

TABLE 11

Survival after Hypophysectomy of Sixty seven Patients

	Average	*Still-Living*
36 with remission	9 3+ mo	21
31 no remission	4 4+ mo	7

strated that objective remission occurs in 50 to 60 per cent of the patients While more time must elapse before conclusions can be drawn analysis of cases of this series in which operation was performed from 24 to 2 5 months ago shows a statistically significant figure of increased survival in patients who responded favorably (Table 11)

DR B J KENNEDY

Surgical hypophysectomy has been carried out at the University of Minnesota Medical School by Drs William Peyton and Lyle French of the Division of Neurosurgery

The rationale for hypophysectomy has been based on animal investigations previous experiences in the hormonal management of breast cancer and postulations regarding the characteristics of breast cancer growth The inhibition of tumors in mice following hypophysectomy has been demonstrated by various investigators[4, 5] Furthermore the administration of growth hormone to animals has produced a number of neoplasms of various organs other than the pituitary gland[6] From the clinical point of view it has been postulated that the favorable effects on breast cancer during administration of androgenic and estrogenic hormones were in part due to pituitary suppression earlier referred to as chemical hypophysectomy [7] It has also been observed that breast cancer has not been reported in patients with Sheehan s syndrome Dr Fuller Albright many years ago suggested that growth hormone might possibly be responsible for some breast cancer growth

The apparent stimulating effect of growth hormone in breast cancer was reported by Dr Olof Pearson[8] I have two patients in whom an exacerbation of prostatic cancer was demonstrated during the administration of growth hormone These data established further criteria for a rationale for total hypophysectomy It was apparent that with present facilities total irradiation of the pituitary gland was impossible Total surgical hypophysectomy was undertaken at the University Hospitals primarily as an investigative tool in the study of breast cancer which would provide a means for further evaluation of breast

as the initial ablative operation in altering endocrine influence on the disease, at least it is preferable to adrenalectomy as a second operation following oophorectomy

The survival period is more than twice as long in those patients who obtain a remission after hypophysectomy as in those who do not

The extent of metastatic breast cancer in patients has been demonstrated by the presence of microscopic metastases in the brain wedge removed and by the presence of metastases in the pituitary itself

Hormonal Replacement

Preoperatively the patients receive 100 mg of cortisone intramuscularly every twelve hours for at least forty eight hours before the operation When patients are treated longer than this, the postoperative course seems even smoother The morning of the operation an additional 100 mg of cortisone is administered orally and 5 mg of desoxycorticosterone acetate is given intramuscularly Postoperatively all medication is placed on an oral basis as soon as possible The cortisone is reduced to an average dose of 50 mg a day

Complications

Certain complications were observed Four patients had rhinorrhea which was temporary in nature This was largely due to puncturing the sinus at the time of rongeuring away the anterior clinoids Meningitis occurred in three patients The first patient had uremia and hypercalcemia preoperatively and continued to be confused postoperatively though the serum calcium decreased to normal The confusion was later proved to be due to an Escherichia coli meningitis The patient died of localized brain abscess The other two patients had a proteus meningitis and a paracolon meningitis Both recovered Loss of smell occurred in one patient This could not be explained since to our knowledge there was no interference with the olfactory nerve All patients have been questioned regarding the loss of sense of smell There were two instances of visual disturbance The first was a

cancer growth and guide future studies in this disease *Though hypophysectomy obviously has produced favor able regressions in breast cancer growth,* the study of hypophysectomy represents a means of perfecting future chemical therapy rather than promoting the surgical pro cedure

Total surgical hypophysectomy has been carried out in twenty two patients followed for more than three months In addition there were two patients in whom extensive dural metastases discovered at the time of craniotomy made it impossible to carry out the surgical procedure This series is not statistically significant It represents *selection of patients based upon theories of breast cancer growth*

Operative Procedure

The scalp incision is made behind the hair line, and the flap retracted forward All the operations were done on the right, except in one case in which there were exten sive metastases on the right The anterior medial portion of the right frontal lobe is removed in a wedge three centi meters wide and extending directly down The procedure provides a direct approach to the pituitary gland and further provides an area of expansion in case cerebral edema should occur In this way postoperative decom pression was avoided No such complication has occurred In those instances in which the optic nerves were short the anterior clinoids were rongeured away to provide better visualization Once the pituitary fossa is visualized the stalk is picked up anterior to the chiasm, clipped and cut The diaphragma sellae is torn by blunt dissection going from the medial portion radially The pituitary is visualized and removed either in small pieces or on oc casion as one large mass

Case 2 This 42 year old woman had had a definite recalcification of osseous metastases six months earlier following oophrectomy At the end of the six months there was exacerbation of the disease with extensive pelvic metastases Following hypophysectomy there was calcification of these osteolytic lesions Fifteen months postoperatively the remission was still maintained

Metabolic studies have been carried out in selected patients Examples of these studies follow

Case 3 Only one of the patients of this hypophysectomy series had had an adrenalectomy This 43-year old woman had been oophorectomized at the time of the radical mastectomy Osseous and pulmonary metastases responded favorably following adrenalectomy One year after the adrenalectomy there was exacerbation of the disease manifested by hypercalcemia and hypercalcuria A total hypophysectomy was carried out This was followed by a decreased serum calcium and a very slow decrease in urinary calcium excretion over a two month period There was a slow increase in serum alkaline phosphatase and concomitant relief of pain Initially there was evidence of spinal cord compression The reflexes returned following hypophysectomy though recalcification of osseous metastases did not occur

Case 4 This patient a 28-year old premenopausal woman had extensive osseous metastases On an intake of 150 mg a day of calcium the urinary calcium averaged 400 to 500 mg daily and hypercalcemia was present One objective of the hypophysectomy was to measure the rate at which an effect in such a patient would occur and to attempt to determine whether or not hypophysectomy would be as rapid in its effect as bilateral oophorectomy Postoperatively there was a rapid decrease in urinary calcium excretion and serum calcium The serum alkaline phosphatase increased there was relief of pain and calcification of osteolytic lesions occurred

Case 5 An extensive metabolic study was carried out

loss of peripheral vision in the right eye The second pa tient six days postoperatively and concomitant with the development of a paracolon meningitis had a loss of vision of the right eye It was felt that the visual loss was sec ondary to the meningitis and not due to trauma Three of the patients have had thrombophlebitis of the leg post operatively There was no subsequent complication Of the entire twenty two patients eleven developed one or more of the above mentioned complications

One patient demonstrated an alteration that may rep resent a complication Postoperatively the patient had re calcification of all osseous metastases The bone flap, however showed progressive reabsorption An attempt to demonstrate metastatic disease by needle aspiration of this flap was unsuccessful This patient was the longest surviving patient and has not had evidence of recurrence within the bone flap that can be demonstrated

Clinical Response

The following are examples of patients undergoing hypophysectomy for advanced breast cancer

Case 1 This 42 year old woman had previously re sponded favorably following oophorectomy There had been calcification of osseous metastases Subsequently there was exacerbation of the disease with multiple osteo lytic defects Total hypophysectomy was carried out and the patient survived twenty five months Relief of pain and recalcification of the osseous metastases were evi dent for twenty months at the end of this time the urinary calcium excretion began to increase The patient re mained asymptomatic for twenty five months postopera tively Because of the recurrent hypercalciuria however the patient was regarded as having a 20-month remission During the remission there was regeneration of the right second rib which had been totally destroyed by the dis ease

creased feeling of well being in seventeen patients It would not appear that pain relief is a result of removing the anterior lobe of the brain There was no response either objective or subjective in four of the patients

Of twenty two patients twelve are dead five of these demonstrated objective regressions Ten patients are alive all having had objective regressions

Mortality

Of the twelve patients now dead seven died because of progression of the cancer some after a period of im provement One patient demonstrating improvement died four days after the family discontinued cortisone therapy One patient died of meningitis as a postoperative compli cation Three deaths occurred immediately postoperative ly two of these patients had bilateral pleural effusion and one had extensive liver and cardiac metastases Such patients would not undergo operation under our present criteria of selection

Regression Data

The average duration of improvement of the patients in this series is very similar to that reported by Dr Ray including those patients still maintaining improvement it has been 7 2 months The average duration of survival of the living patients of which there are ten has ranged from three to twenty five months the average period be ing 9 4 months The longest survival time of the patients who died (the other twelve patients) was less than thir teen months This included two patients dying two and four days postoperatively The average survival of this group is four months The duration of survival of the en tire series at the present time ranges from two days to twenty five months The average survival has been 7 3 months

in this 46 year old woman The purpose of this study was to measure the extent to which 50 mg of cortisone would affect metastatic cancer in the hypophysectomized patient Before hypophysectomy the patient was placed on a controlled constant intake and urinary calcium serum calcium and serum alkaline phosphatase determinations were done Following administration of 50 mg of cortisone daily there was an increase in calcium excretion suggesting that the cortisone was initiating an acceleration of the disease in the bones The dose of cortisone was then increased to 300 mg daily Calcium excretion decreased but she still remained in negative calcium balance The serum calcium decreased to a normal range It was postulated that this negative calcium balance was a result of the decalcifying effect of cortisone at the larger dose levels and the cancer was in part inhibited by the larger dose of cortisone

Subsequently a total hypophysectomy was performed with the patient maintained on the same dose (300 mg) of cortisone There was no obvious alteration in the serum calcium or calcium balance Since the pituitary was absent it was postulated that the persistent negative calcium balance either was due to the decalcifying effect of cortisone or that cortisone in small amounts maintained a certain rate of tumor growth Only a slight rise of serum alkaline phosphatase occurred Finally after approximately one month the cortisone was reduced to 50 mg daily Immediately there was a rise in serum alkaline phosphatase and a positive calcium balance was achieved Subsequently there was recalcification of the osseous metastases

Summary of Clinical Results

The results in this series of hypophysectomized patients are not statistically significant, since the series consists of of group of selected patients Objective regressions occurred in fifteen of twenty two patients There was no objective response in seven There was pain relief or in

creased feeling of well being in seventeen patients It would not appear that pain relief is a result of removing the anterior lobe of the brain There was no response, either objective or subjective in four of the patients

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We performed our first hypophysectomy in January, 1952 our enthusiasm waned abruptly, however, after experience with three or four cases and it has only been within the last year that this study has been resumed This entire project has been under the supervision of Dr Francis Moore the Chairman of our Department of Surgery and closely supervised by Dr Andrew Jessiman We have received close cooperation and much assistance from Dr Kendall Emerson of our Medical Department in particular and many other people in the hospital The first patient that we operated upon a woman with cancer of the ovary demonstrated no evidence of any alteration in the course of her disease We also have performed hypophysectomies in one patient with cancer of the testicle one with prostatic cancer and one with cancer of the adrenal In none of these was there evidence of significant alteration of the disease although these patients did experience some pain relief and some increased sense of well being

One patient was operated upon for diabetes mellitus with vascular renal and retinal disease and thirteen patients were operated upon for metastatic mammary carcinoma eleven of these within the past fourteen months Our experience with hypophysectomy is therefore limited to eighteen patients

Operative Procedure

Patients are operated upon under light general anesthesia with nitrous oxide through endotracheal tube with the addition of muscle relaxants We have not used ether or induced hypotension in any patients in this group The right frontal bone is exposed by a coronal incision

In conclusion, each investigator has to choose a method of therapy for breast cancer patients In our experience all patients who responded to therapeutic oophorectomy were improved by hypophysectomy Two patients who improved following hypophysectomy subsequently dem onstrated another regression with androgen therapy *Estrogenic hormone therapy has failed to affect the disease* in six patients demonstrating reactivation of the disease after transient improvement following hypophysectomy In the postmenopausal patient estrogenic hormone ther apy would appear to be the preferential treatment The decision as to whether or not a woman is postmenopausal is based upon the degree of ovarian function most usually measured by the vaginal smear which usually shows cornification five years or more after the last menstrual period It is possible that hypophysectomy would be of value in those patients in the postmenopausal group who have obtained regressions from estrogenic therapy

to them We have done this in only one patient, operated on approximately eight weeks ago

Hormonal Replacement

Patients are prepared with cortisone previous to opera tion Those already receiving cortisone are given an increased amount just prior to operation All of these pa tients have been started on intravenous compound F after the gland has been removed usually receiving 150 to 200 mg during the first twelve hours I think in every case we have switched directly from the intravenous Cortef to oral cortisone within twelve hours of operation The cortisone is then diminished usually to a level of 50 mg within a week to ten days after operation We have never been able to carry any patient on less than 50 mg of cortisone per day even when gradual reduction has been attempted the patients have always experienced extreme fatigue hypotension etc

Mortality

Two patients in our series of eighteen have died within thirty days of operation without leaving the hospital One of these patients died of strangulation from a huge mediastinal mass causing acute bronchial obstruction She also had an acute myelophthisic anemia due to virtual replacement of her bone marrow with tumor tumor cells were actually seen in a smear of circulating blood It was felt that her overwhelming disease and not the operation was the cause of death

The other patient who died within thirty days also had extensive pulmonary and pleural lesions She died of an aspiration pneumonitis seven days after operation in what I think must be considered an operative death

Among the other sixteen patients six died from one to

and the bone flap is carried to the midline and as low as possible As the dura is opened 30 to 40 cc of spinal fluid is drained The right olfactory tract is sacrificed as Dr Ray outlined The pituitary stalk is exposed between the optic nerves and cut At first we exposed the stalk rather high up putting our silver clip on it coagulating distal to this and cutting through the coagulated area In the last five cases, in an effort to combat diabetes insipidus I have made a special effort to free the arachnoid as carefully as possible completely avoiding the stalk, and have simply placed a nerve hook around the stalk gently and cut it without any clipping or coagulation There has been very little bleeding A small pledget of cotton on a silk string is used to tuck the stalk back under the chiasm This is left in place until the operation is finished and then removed We try not to touch the proximal stalk or have it handled during the operation After removing the gland as thoroughly as possible by dissectors and curettes we wipe the sella briskly with dry cotton and swab it thoroughly with Zenker s solution

In the last patient treated we sutured a piece of polyethylene film over the surface of the sella turcica tacking it to the margin of the diaphragm of the sella at the conclusion of the operation It has been shown in rabbits that if small amounts of pituitary tissue are left in the sella within ten days to two weeks after hypophysectomy one can trace new vessels growing down from the portal circulation from the brain into the sella to revascularize the remaining cells [9] Since it is possible that the function of the anterior pituitary gland is under the control of receptors in the hypothalamus it may be that if a few cells are left behind we can reduce their activity or at least delay their regeneration and resumption of function if we can minimize the return of blood supply

One-half of our patients that is nine developed diabetes insipidus requiring continuing treatment with pitressin tannate in oil Six patients had no diabetes insipidus or at least not enough to require any treatment and the three remaining had only very transient or mild diabetes Three of the five patients in whom the stalk had been cut without any clipping or cautery did not develop diabetes at all Four of these five patients interestingly enough on testing with nicotine and hypertonic saline showed that they still have the capacity to secrete antidiuretic hormone The fifth patient has not been tested

It is certainly a clinical impression that low stalk section without clipping cautery, or any trauma to the upper stalk is going to result in a decrease in the incidence or at least in the severity of diabetes insipidus We do not yet know however whether or not this procedure is going to result in leaving anterior pituitary cells in the lower end of the stalk We have the impression that the stalk varies considerably in size from one patient to another and I do not know the significance of a thickening of the stalk just above the sella We have seen gross evidence of metastatic cancer in the pituitary in three of thirteen patients with cancer of the breast

Laboratory and Clinical Studies

Among ten of the patients with breast cancer who have had adequate testing uptake of radioactive iodine varied from 15 5 to 56 per cent and postoperatively from 1 to 16 per cent Among the last seven patients who are the most satisfactory cases from a surgical point of view the uptake of radioactive iodine postoperatively has never been higher than 6 5 per cent PBI values have been between 1 3 and 3 FSH assays in the breast cancer patients showed preoperative values of 10 to 200 mouse

five months after operation of progression of their cancer The remaining ten are still alive from eight to thirteen months after operation Of these ten, one is the diabetic patient and the other nine are mammary cancer patients

Morbidity

We have been impressed with the low morbidity of the procedure Most of the patients have been alert within two to four hours after the operation and able to take fluids and cortisone by mouth the following day in per fectly adequate amounts

Complications of surgery have been rare One patient developed a wound infection due to technical error in the handling of an open frontal sinus There has been no men ingitis no rhinorrhea There have been no intracranial hematomas and no hemiplegias one transient weakness of the left arm We have had no visual disturbances in the way of visual field defects or diminished visual acuity in our patients with the exception of the diabetic patient who was essentially blind at the time of operation Two or three of our patients have complained rather bitterly of the loss of smell One patient had a mild seizure the day after operation and we have had three other patients who had single convulsive seizures one six weeks one eight weeks and one ten months after operation This ex cludes the diabetic patient who had many convulsions in the period six to twelve weeks following operation I understand this has also been your experience Dr Luft in diabetic patients Another complication seen in one of the two patients in our series who had been treated previously by adrenalectomy was two episodes of acute severe hyponatremia We have not seen any difficulty in sodium or other electrolyte regulation in any of the hy pophysectomized patients who still had adrenals in place

taken thirty minutes after the stalk was cut showed complete disappearance of all the ACTH in the circulating blood This was also true in samples taken after the hypophysis was removed

Clinical Results

Of the thirteen patients with mammary cancer who are still living the longest survival thirteen months is that of a male patient This patient who has had the most satisfactory subjective and objective remission observed so far was previously treated by orchiectomy to which he had an equivocal response Following hypophysectomy he has had extensive recalcification of osteolytic lesions throughout the spine and pelvis He has been completely free of bone pain since the day of operation and his condition has been very satisfactory throughout

Four of our thirteen patients have been failures two died in the postoperative period and two failed to show any halt in the course of the disease All four of these patients had extensive pulmonary and pleural lesions and widespread soft tissue lesions Two of them had liver lesions as well It is too soon to give any statistically valid results on our other nine patients At least three of them have had striking objective remissions and are still in remission At least three others seem to have marked arrest of a rapidly advancing disease process It is possible that the nine surviving patients will show objective relief of significance As to subjective relief it is difficult to grade and probably one should not even try but I would say that in a third to a half of our patients the subjective relief has been very great and in the other half it has been mild but definite One question that I am hoping those of you who have had longer follow ups will discuss is how many of these patients are actually returning to

units Postoperatively the values were five units or less in all but one who had a positive FSH of 7 5 mouse units

In patients with bony metastases we have done urine calcium excretion studies on low calcium diets All patients with bony metastases have not shown increased calcium excretion With only one exception however, when in creased calciuria was present it diminished following hypophysectomy Preoperative estrogen stimulation stud ies were found to be very disturbing to some of these patients They may develop fever tremendous malaise and increased bone pain and one or two patients have gone into coma

In our experience whether or not a patient responds to cortisone has not proved to be satisfactory indication of what hypophysectomy will accomplish from a thera peutic point of view Certainly some patients who have not shown decreased calciuria on up to 300 mg of corti sone preoperatively have still obtained some reduction in calciuria after hypophysectomy

Dr David Hume of our physiology group has been carrying out bio assays of circulating ACTH in some of our patients He has found that stimulation of ACTH production is markedly reduced when the pituitary stalk is cut Almost all of our previous patients have received some cortisone preoperatively The last patient however had not had any cortisone for a period of two to three months before operation She was given no preoperative cortisone and none during the first part of the operation Following craniotomy the stalk was exposed but neither the stalk nor the gland were touched A sample of the arterial blood was taken Bio assays made with it on hy pophysectomized dogs with the adrenal vein cannulated showed a large amount of circulating ACTH presumably as the result of the trauma of the craniotomy Samples

DR LEONARD P ELIEL

The work which I am presenting has resulted from the collaborative efforts of the Oklahoma Medical Re search Foundation and the Department of Neurosurgery of the University of Oklahoma School Medicine Since July, 1955 we have done nine craniotomies in patients with advanced carcinoma six of which were surgical hypophysectomies for advanced carcinoma of the breast and three of which were craniotomies for instillation of radioactive isotopes in patients with advanced prostatic cancer We will discuss the latter tomorrow

The technique that has been used in Oklahoma City for hypophysectomy is essentially that which Dr Ray has described The patients are usually anesthetized with nitrous oxide although light ether anesthesia with pento thal induction also has proved satisfactory in a few cases The stalk has been cauterized in all the cases reported here

Hormonal Replacement

We have tried in two cases to maintain the patient with intravenous soluble hydrocortisone only rather than with intramuscular cortisone This technique was found un satisfactory because of the marked fluctuations in blood pressure necessitating frequent regulations of the intra venous drip Two attempts to maintain patients post operatively on prednisone have proved unsatisfactory with the patients developing weakness gastrointestinal symptoms and general malaise I would be interested to hear if any other conferees have had any experience with this steroid as the sole maintenance therapy

Mortality and Morbidity

There was one postoperative death which occurred two weeks after hypophysectomy as a result of progres

jobs or to housework We have been impressed that some of these patients who seem to have both subjective and objective improvement with clear evidence of regression *of disease are still not interested in doing very much*

If any summary can be made from our clinical experience to date, it is that this operation seems to be entirely feasible with low morbidity and mortality The patients all feel better the next day and are glad they have gone through with the operation The relief of pain and the increased sense of well being has been very rewarding regardless of whether or not there has been any demonstrable alteration in the disease course

There are certain disadvantages to the procedure Certainly the loss of smell is a minor one The problem of diabetes insipidus is a definite one which requires regulation and management We may be able of course to control that better with more surgical knowledge The patients who have had adrenalectomy plus hypophysectomy are difficult patients to manage postoperatively, and I believe that it is probably not feasible to care for such *patients except in the hospital*

sectomy include absence of urinary FSH a drop in radio active iodine uptake in twenty four hours to 5 per cent or less and a drop in protein bound iodine to 3 micro grams or less Later on I will present some other physio logic tests which I think may also be some indication of completeness of hypophysectomy

I would like to discuss the failures in a little more de tail One of these patients who was considered to be com pletely hypophysectomized from the physiologic point of view was a patient of 54 years who had an unequivocal regression of tumor after the administration of testoster one and who upon administration of estrogen had shown unquestionable acceleration of tumor growth This patient did not obtain a remission following hypophysectomy The hypophysectomy was easy and it was the feeling of the operator that there was no residual tissue However at death the sella was excised en bloc serial sections made and a few sheets of viable pituitary cells were shown to be present This raises the very interesting question of course as to whether or not a few viable pituitary cells can maintain tumor growth even in the presence of physiologic tests which indicate virtual absence of pitui tary function One 49 year old patient with osseous me tastases who had obtained a remission after oophorectomy two years previously failed to obtain a remission after physiologically complete hypophysectomy Two of the patients who failed to respond had incomplete hypophy sectomies Each had very close approximation of the clinoids leaving only a small aperture Our group has not had the courage to rongeur away the anterior clinoids for fear of getting into the sphenoid sinus

One patient preoperatively had mild diabetes charac terized by slight elevation of blood sugar and intermittent glycosuria not enough to require the administration of

sive disease All of our patients developed diabetes insipidus Our only other complication was a temporal visual field defect which persisted postoperatively

Clinical and Laboratory Results

The longest survival in our very recent series is now about seven months with the patient still in excellent remission Of the two remissions (Table 12), one is classified as excellent, meaning actual objective evidence of tumor regression and one as partial which corresponds to arrest of disease with a fall of urine calcium excretion to normal values and no radiographic evidence of progression Completeness of hypophysectomy is judged by physiologic testing Our criteria of complete hypophy

TABLE 12

Surgical Hypophysectomy for Carcinoma of the Breast in Six Patients

	No Pts	Induced Remission		Induced relapse with estrogen	Hypo-X Complete (Physiologically)
		Oophorectomy	Testosterone		
I Remissions					
Excellent	1	+	Not done	Not done	Yes
Partial	1	Not done post menop	Equiv	Not done	No
II Failures	1	Not done post menop	0	Probable	No
	1	+	Not done	Not done	Yes
	1	Not done post menop	+	+	Yes
	1	Not done post menop	0	Not done	No

Postoperative mortality 1 patient two weeks postoperatively from progression of disease

+ Indicates remission produced

0 No remission produced

DR SAMUEL G TAYLOR, III

Our group has attempted hypophysectomy on eleven patients The operations were done by Dr Wesley Gustafson University of Illinois, and Dr Adrien VerBrugghen of Presbyterian Hospital Chicago both highly qualified neurosurgeons Of the eleven cases in which hypophysectomy has been attempted, it was completed in nine Two patients were inoperable one because of an anatomical variation that would have required sacrifice of the optic nerve which we did not feel was justified and the other patient because of cerebral metastases that were in the way We had one surgical complication resulting in a loss of vision except on the nasal side of the right eye this patient no longer has adequate vision We have three operative deaths Two were due to surgical trauma and one to renal shutdown on the eighth postoperative day in a patient with extensive liver metastases

Clinical Results

The three patients who died did so before there was any evidence of tumor regression Two patients have had very remarkable definite and outstanding regressions The other four patients have not shown any regression Neither of the patients who responded favorably had had any form of therapy for their metastatic disease before the hypophysectomy Both were premenopausal The first patient a woman of 43 had a tremendous primary tumor in situ that extended to the axilla She also had osseous metastases The tumor to all intents and purposes had disappeared Sixteen months have passed without any evidence of recurrence The other patient is a 35 year old woman who had osseous and pleural metastases which necessitated emptying the chest weekly or at biweekly

insulin After hypophysectomy, which was physiologically complete this patient had a normal fasting blood sugar and no further glycosuria

I would like to reiterate the feelings of Dr Matson Dr Kennedy and Dr Ray that this is a procedure which in the hands of competent neurosurgeons is certainly easy to accomplish In this particular group even though it is our first six cases of surgical hypophysectomy the results have been very gratifying not in terms of remissions but certainly from the point of view of their post operative course

DR. WILLIAM H BAKER

We have not been completely successful in removing the total hypophysis Our first patient was done early in 1951 on the advice of Dr Fuller Albright and that patient had a functioning adrenal carcinoma She was a 22 year-old female with Cushing s syndrome, including acne hypertension elevated ketosteroids and formalde hydogenic corticoids and polycythemia Studies done prior to hypophysectomy showed that this tumor was responsive to large amounts of ACTH and on 500 mg of ACTH daily she had an increase of 17 ketosteroids and formaldehydogenic corticoids Her pituitary was removed without instillation of Zenker s fluid and about 0 7 gram of pituitary tissue was removed Following operation the levels of all the previously elevated steroids decreased to normal levels within twenty four hours In addition her hypertension lessened and in fact disappeared after fif teen days However a gradual increase in her 17 keto steroids then appeared accompanied by an increase in her formaldehydogenic corticoids and then there was a gradual increase in her hypertension and acne Four months after operation she died An autopsy revealed metastatic adrenal carcinoma involving the liver and lung The fossa contained about 0 7 gram of pituitary tissue and a microscopic examination showed active mi tosis in many of the cells probably representing active regeneration

We abandoned this procedure until the report by Dr Olivecrona and Dr Luft of their excellent results in pa tients with breast cancer

At the present time we have hypophysectomized seven patients six with breast cancer and one with melano carcinoma The patient with melanocarcinoma received

intervals Since hypophysectomy, there has been no accumulation of fluid She has been in remission for fourteen months

DISCUSSION

Dr Lipsett Dr Luft what is the lowest value you can get and be sure you are measuring ketosteroids?

Dr. Luft This is a difficult question to answer I would think about 1 to 2 mg

Doctor Did Case 16 (p 7) have evidence of adrenal pituitary function?

Dr Luft The excretion of 17 ketosteroids was 2 8 mg while she was on cortisone That is a low value The ACTH test was negative all the time

Dr Kennedy What type of response did she have? Was the pain relieved?

Dr Luft The pain was relieved She had a marked decrease in the infiltration in the left breast where she had her primary tumor She had a wound in the skin over the primary tumor that was very painful before the operation The wound did not disappear completely

Dr Kennedy Dr Ray could I ask you why you drain the spinal fluid?

Dr Ray The drainage allows further retraction of the brain

Dr Kennedy You are emptying the ventricles?

Dr Ray We drain all the spinal fluid but not until the dura is opened From time to time we remove an additional amount during the operation One of the reasons for this is to get a "slack brain and often once the field is exposed I can remove the retractor and work without it The other advantage of draining the fluid is that the field in the region of the sella is kept dry

Doctor Are antibiotics used?

Dr Ray Yes if the sinuses are opened Also all patients are given anticonvulsants for about ten days since seizures may occur during this time

Dr Kennedy Are convulsions frequent?

Dr Ray I would not say they are frequent They occur in possibly 5 per cent of the patients no more than that

Dr Kennedy Do you cut the olfactory nerves?

Dr Ray The right olfactory nerve is divided If the left nerve pulls away and tears as it may then patients lose smell function I do not know exactly how many patients have lost the sense of smell We perhaps have not followed this as carefully as we

no benefit and there was no effect on the course of the disease the patient died four months after the operation with a widespread melanocarcinoma of the lungs and brain Functioning pituitary tissue was again found in the sella Six patients with cancer of the breast were hypophysectomized who had not had a previous ovariectomy or adrenalectomy and all of whom were five years postmenopausal or post bleeding Of these six four represented incomplete removal of the hypophysis and were unsuccessful as judged by physiological tests after the operation and corroborated by autopsy

Two patients did show complete hypophysectomy as measured by protein bound iodine determinations and inability to respond to epinephrine as measured by blood eosinophils In both of these latter patients there was little change qantitatively in their urinary output of 17 ketosteroids corticoids or estrogens as measured by fluorogenic phenols They were both maintained on 50 mg cortisone daily and in both cases androsterone and etiocholanolone completely disappeared from their urine

A similar disappearance of androsterone and etiocholanolone was encountered in adrenalectomized patients maintained on cortisone

We are unable to demonstrate any change in chemical measurements of estrogens either as fluorogenic phenols or by countercurrent distribution In both of these latter patients follicle stimulating hormones disappeared after operation

DOCTOR You dont relieve the edema?

DR RAY Edema has not been an important factor and the wound is closed without decompression

DOCTOR How quickly do the tumors regress within a few days?

DR. RAY No we sometimes do not see an obvious regression in a lesion for three weeks or more

DR KENNEDY Could you tell me whether the pituitaries of your patients who have been previously castrated appear any larger grossly than patients who have not been castrated?

DR RAY I dont think we would be able to answer that, unfortunately While we have sometimes weighed glands some tissue is lost in suction Pituitaries vary in size just as noses do It brings to mind also the fact that we have come to recognize usually at the table those who have metastases in the gland Do you know how many there are Dr Lipsett?

DR LIPSETT Six of our patients have had metastatic nodules in the pituitary

DR ADAIR How did you recognize them?

DR RAY You can tell usually by the gross appearance of the tissue

DR BERGENSTAL Dr Kennedy what is your interpretation of the data obtained in your Case 5 (p 29)?

DR KENNEDY The interpretation of these data was that 50 mg of cortisone may initiate a stimulating effect on the breast cancer This has been seen during the initiation of therapy with androgenic and estrogenic hormones However with the latter hormones persistence in hormone therapy may be followed by a remission It is quite possible that had the 50 mg of cortisone been continued a similar type of remission would have occurred Certainly during the period the patient received 300 mg there is indication that the growth rate of the cancer was partially suppressed Yet at the same time there may be a mild degree of maintenance of a growth rate because of a mild stimulating effect on the tumor In other words cortisone may have a dual effect 1) that of suppressing the pituitary and adrenal glands with respect to a stimulating factor of breast cancer and 2) supplying at the same time as metabolic breakdown products substances that are also stimulating to the breast cancer Certainly after hypophysectomy it is evident that reduction of cortisone to 50 mg a day is followed by objective evidence of improvement Clearly therefore the 50 mg of corti

might but the patient who does lose the sense of smell is usually not greatly upset by it

DOCTOR How about the loss of taste sensation that goes with it?

DR RAY *They do not lose taste*

SAME DOCTOR Only smell?

DR RAY Taste is one thing smell is another Taste is preserved that is they can discriminate among salt bitter sour and sweet There are also other aspects to enjoying food such as savoring its consistency

If the stalk is not coagulated diabetes insipidus which requires pitressin is less likely to develop We think there usually is some degree of change in fluid balance that can be measured on testing Fluid intake may increase to 2 000 to 2 500 a day but patients can easily handle this amount without the need for pitressin

DR M B LIPSETT Are you disturbed by those cases in which the stalk is very broad?

DR RAY I am because there is the po sibility of leaving anterior lobe cells but maybe the cells are not important The diabetes insipidus is not an unsurmountable complication but it is a nuisance Probably between 40 and 50 per cent of our patients thus far have required pitressin

DR KENNEDY Was there increased intracranial pressure in those patients who had clots?

DR RAY For the first twenty four hours after operation patients usually look well In the beginning we transferred every patient back to Memorial Hospital from New York Hospital on the day of operation The afternoon of operation patients look well and they are able to have visitors that night During the night or the next day they may develop signs of progressive drowsiness or stupor and some left sided weakness as the result of an intracranial clot Usually this complication comes on within the first forty eight hours For the past few months we have not transferred the patients for the first two or three days after operation and we have picked up two clots in that time

DOCTOR Is it sometimes true that there is this picture without clot being present?

DR RAY The patients upon whom we have re opened the wounds have all had clots and the patients listed as "dying from surgical complications" all had clots either extradural or subcortical

lytic lesions to undergo spontaneous conversion to osteoblastic If such change does occur it would tend to invalidate radiological evidence of recalcification as a criterion of response to treatment

DR KENNEDY Much of the data are based on clinical and x ray findings Actually pathological data are required to answer these questions Certainly an osteolytic lesion if the rate of growth is reduced might appear osteoblastic but the lesion may still be growing In other words the rate slows so that there can be osteoblastic activity about the lesion On x ray it looks more calcified This would represent an osteolytic changing to an osteoblastic lesion but it is still growing So it is really not under control On the other hand with an osteolytic lesion and a decrease of the urine calcium to a normal level a more normal bone structure or highly calcified structure may occur Biopsy will reveal bone with an occasional trapped tumor cell In contrast to the previous type where a little calcium is deposited around the tumor those tumor cells usually are quite active This is my interpretation of this phenomenon based on metabolic changes supported by bone biopsies

CHAIRMAN PEARSON The physiologic effects of cortisone in large doses on normal bone is to produce osteoporosis and negative calcium balance If cortisone in a patient with an abnormal bone condition who has high calcium excretion puts the patient in positive calcium balance then you cannot reconcile this with any known effects of cortisone on normal bone Therefore I think that you must interpret it as positive evidence of suppression of bone destruction You infer that if the destruction had been due to tumor that the progress of the tumor has subsided Measurement of calcium excretion is like any other test it is like the x ray They are all indirect tests and you have to use inference

DR TAYLOR This is such an important point that I think we ought to have some information on the effects of cortisone in other metabolic diseases in which you have a high calcium excretion and high serum calcium

CHAIRMAN PEARSON It has been studied There are many cancer patients in whom cortisone has no effect at all on high calcium excretion

DR KENNEDY Having established the fact that this patient did have a regression in terms of calcification of bones the interpretation is that cortisone is good hypophysectomy is better

DR. FORREST Following implantation of the pituitary with

sone used as maintenance therapy is not responsible for the type of regression that is being observed after hypophysectomy

Dr Bergenstal That brings up the whole question of whether or not cortisone can be converted to substances that have estrogenic activity

Dr Kennedy You can go one step further Androgens can be converted to estrogen

Dr Bergenstall Estrogenic activity by bio assay was found in the urine of patients after a dose of cortisone

Dr Kennedy This was one of the postulations we considered working on and possibly explains the initial increase in calcium excretion but regardless it would seem that the 50 mg after hypophysectomy is not doing any damage to the patient It does not appear to be responsible for the remissions and therefore removing the pituitary would appear to have been the factor responsible for the regressions

Dr Taylor Aren t we making a mistake in relating the decrease in calcium excretion to tumor regression? Might it not be the effect of cortisone on normal bone?

Dr Kennedy The 300 mg of cortisone may produce a decalcifying effect since the negative calcium balance was maintained Actually the serum calcium did come down to normal ranges The answer to that question is not yet clear

This study was reduplicated using prednisone in a patient of the same age A dose of 250 mg a day produced an almost identical effect

Dr Eliel We can show you a metabolic study which is almost the exact duplicate of that one except that the patient was not hypophysectomized and an excellent remission was achieved with 75 mg of cortisone I still don t think that it is clear that the re mission is the result of hypophysectomy I still think it might be due to the cortisone

Dr Taylor You cannot call it remission I think it is wrong to call it remission It is a metabolic change How do you know it is remission of the disease in the bone? Why isn t that an effect on the bony system instead of necessarily on the tumor?

Doctor You might go one step further Maybe you just changed the tumor to a blastic type of lesion

Dr Forrest I had the impression that it was rare for osteo lytic and osteoblastic lesions to occur simultaneously or for osteo

to suppression of ovarian function The patient in the postmeno pausal age group who has responded to estrogenic or androgenic hormone therapy with subsequent exacerbation is regarded as an other candidate for hypophysectomy Two patients in this group have demonstrated regressions The latter consideration is based on the theory that estrogenic and androgenic hormones in postmeno pausal women inhibit the pituitary function in part and this is responsible for regressions of the breast cancer Subsequent re activation of the disease in these patients may represent an escape of the pituitary from the inhibitory effect of the hormones A few patients were selected for operation who had not responded to castration In such patients no response was anticipated and the results justified this opinion Hence very few hypophysectomies have been carried out in patients previously castrated for recurrent disease who did not show a response to the castration As previous ly mentioned therefore the selection of patients in this series for hypophysectomy makes the series not statistically significant

Doctor Have you operated on any patients who failed to re spond to estrogen?

Dr Kennedy No

Dr Jessiman In relation to what Dr Kennedy said about the response to hypophysectomy as judged by calcium excretion studies I would like to say that many of these patients have shown a response not manifest until some four or five weeks after the operation as compared to the almost immediate responses that we frequently see with ovariectomy

Dr Rhoads How many of your patients have had oophorecto my and adrenalectomy?

Dr Matson Just one The other adrenalectomy was a prostate cancer patient

Dr Rhoads You are really not in a position to say whether or not hypophysectomy has a role beyond that of adrenalectomy?

Dr Matson We are not able to say

Dr Ray They had all been castrated?

Dr Matson Yes

Dr Ray What were their ages?

Dr Matson We have not done any patients ten years post menopausal at all

Dr Rhoads One more question do you feel that this procedure is any more difficult to perform than an adrenalectomy?

Dr Matson Much less difficult in the experience of our hos

radon cortisone is not required for the first two or three postoperative weeks Several of our patients with skeletal metastases have shown a falling serum calcium and rising alkaline phosphatase which commenced two to three days after the implant and coincided with relief of pain These changes could not have been due to cortisone for they had not had any We do not regard these changes as evidence of regression of disease unless they are later followed by skeletal recalcification

DOCTOR Dr Kennedy s cases are very carefully selected Is this true of yours Dr Ray?

DR RAY I did not mention the type of case that we exclude One of these is the patient with evident intracranial metastases We have included some who have had metastases to the skull and have cranial nerve palsy but no one who has increasing hemiplegia aphasia or increased intracranial pressure We exclude those with impaired liver function due to extensive liver metastases We also exclude the patient whose pulmonary metastases are so great that the lung capacity is limited to the degree that they are unsafe for operation

DR KENNEDY Dr Ray I agree with you We do not operate on anybody with bilateral effusion or with extensive liver metastases If the patient will not survive there is little to be gained by hypophysectomy

DR RAY We were pleasantly gratified by our results in patients who had a lot of pleural fluid In many of these the fluid has not reaccumulated after operation If we can show that the lung capacity is adequate with the fluid drained we do not regard pleural fluid as a contraindication to operation

DR KENNEDY We operate on those who have unilateral effusion but not those with bilateral effusion In our experience they will continue to be ill with pulmonary disease

DR JESSIMAN Dr Kennedy on what grounds did you select your patients?

DR KENNEDY The patients were selected for operation by the following criteria The patient who was therapeutically castrated for recurrent disease and demonstrated an objective improvement was regarded as an ideal candidate for hypophysectomy Patients undergoing a spontaneous menopause during the time of recurrence of the disease frequently have a slowly progressive course Up to three years after the last menstrual period such a patient will respond to hypophysectomy This result of course could be due

to suppression of ovarian function The patient in the postmeno pausal age group who has responded to estrogenic or androgenic hormone therapy with subsequent exacerbation is regarded as an other candidate for hypophysectomy Two patients in this group have demonstrated regressions The latter consideration is based on the theory that estrogenic and androgenic hormones in postmeno pausal women inhibit the pituitary function in part and this is responsible for regressions of the breast cancer Subsequent re activation of the disease in these patients may represent an escape of the pituitary from the inhibitory effect of the hormones A few patients were selected for operation who had not responded to castration In such patients no response was anticipated and the results justified this opinion Hence very few hypophysectomies have been carried out in patients previously castrated for recurrent disease who did not show a response to the castration As previous ly mentioned therefore the selection of patients in this series for hypophysectomy makes the series not statistically significant

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Dr Matson Much less difficult in the experience of our hos

pital where a good many adrenalectomies are done for various reasons

There is one other thing I did not mention This procedure is not something for the itinerant neurosurgeon to do once or twice a year It should be done in a center by a neurosurgeon cooperating in a well organized project not as an occasional technical exercise

Dr Bergenstal When adrenalectomy was first considered I remember Dr Huggins statement This will be something we will never be able to do except in centers where we have a topnotch team of internists and surgeons Now as we have had increasing experience with the operation and found the ease with which it can be done many small centers with good internists good surgeons can successfully carry out this procedure I think it is again a matter of experience Four or five years have shown us what we can do The same thing I believe would happen here too

Dr Ray If hypophysectomy is going to be done in poorly staffed hospitals it is sure to fall into disrepute I would expect that most well trained neurosurgeons can do the operative job but a poorly trained one is sure to get into more trouble than is warranted On the other hand you can never regulate that kind of thing or insist that an operation is so technically difficult requires such skill that it can only be done in a few hospitals

Dr Bergenstal At this phase we must try all types of cases of breast cancer because I dont think we are in any position to select cases as yet We have no idea what we are doing with hypophysectomy whether we are doing more than with oophorectomy or adrenalectomy Until we can get a large number of cases of various types and groups of carcinoma we are not going to *know what potential we have here*

Dr Kennedy From Dr Rays data and our own we do know that the majority of patients who respond to oophorectomy are going to improve with hypophysectomy I am convinced of this This is a therapy I can offer the patient In other types of patients we dont know There hypophysectomy is a research procedure which should be done but it should be selective and carefully considered

Dr Matson Is that correct? Is it true Dr Pearson except for the patient who has gotten a good response to oophorectomy you at the moment have no preoperative criteria as to whether or not a patient may get a good result from hypophysectomy?

CHAIRMAN PEARSON I think that is true There are a few other things besides response to castration which make us feel that the patient has a good chance The patient who responds favorably to testosterone we think is likely to get a good response to hypophy sectomy We cannot demonstrate that statistically at the moment with a larger number perhaps we can Exacerbation of the disease by estrogen is felt to be a good criterion Again statistic wise we need more information because we don t believe that a test of estrogen in all patients is a wise thing it may lead to serious trouble

DR KENNEDY I would like to ask a question about estrogen stimulation of the tumor There is a case that Dr Ira T Nathanson and I studied back in 1948 This 63 year-old patient was given stilbestrol immediately had exacerbation of pain developed hy percalcemia and was very ill According to Dr Kendall Emerson this represents stimulation of breast cancer

DR JESSIMAN What dose?

DR KENNEDY 15 mg a day In the face of persistence of therapy this patient had regression of pulmonary metastases re gression of osseous metastases and the subsequent calcium balance study demonstrated a positive balance The hypercalcemia dis appeared The testing of tumors to establish estrogen dependence is misleading

DR. JESSIMAN Don t you think that such a result will be seen in 5 per cent of the cases only?

DR TAYLOR No

DR KENNEDY I think this is too specific to be regarded as a coincidence

DR JESSIMAN Is there another patient like this?

DR KENNEDY Not that I have ever studied

DR TAYLOR I have not done calcium balance studies on such a patient but I have seen cases in which patients have been given estrogen and the soft tissue lesions have progressed and the patient has had an increase in bone pain Then if estrogens are continued after about two weeks definite regression of disease may occur I don t think this is uncommon I don t think that you can discard estrogen therapy on the basis of a short term observation

CHAIRMAN PEARSON I agree that the only definite criterion we have for the selection of patients at the moment is the response to castration The other things are suspicions

DR TAYLOR Unfortunately response to castration is not imme-

diate you have to wait about three months before you can make a decision on this basis

Dr Bergenstal What about patients who are already in spontaneous menopause? There our criteria for castration are gone

Dr Jessiman You can use the stimulation test perfectly well in the postmenopausal woman to find out whether or not she has a "hormone stimulated tumor We prefer this term to "dependent."

Dr Taylor How long do you continue this test?

Dr Jessiman For about three days

Dr Kennedy Then you would have discarded the patient I described who did not improve under estrogen therapy for some time

Dr Jessiman No I should have said that this woman had a hormone stimulated tumor a tumor that could be stimulated by estrogen and that therefore she would then possibly respond to hypophysectomy

Dr Taylor Let us put it this way the tumor is stimulated by estrogen the estrogens suppress the pituitary regression occurs

Dr Jessiman That is what happened in this case but all we are trying to do is pick out the hormone stimulated tumor as opposed to the entirely autonomous tumor which goes on irrespective of ablation therapy Dr Kennedy has shown us a very nice test Your patient had a hormone stimulated tumor and probably would have done well with hypophysectomy You did a hypophysectomy *on her with estrogens*

Dr Eliel On the other hand estrogen is an extraordinarily dangerous thing to give in estrogen dependent tumors and in the presence of osteolytic metastases might lead to hypercalciuria and hypercalcemia

Dr Taylor It is not such a dangerous thing to give Fifty per cent of women well past the menopause will show objective regression with estrogens It is good therapy

Dr Eliel In 50 per cent it will stimulate the tumor I don t think we should persist

Dr Lipsett *I don t think it is possible in discussing estrogen* therapy to group premenopausal and postmenopausal women together As you demonstrated Dr Kennedy some of the women respond to estrogen and respond to hypophysectomy In the premenopausal women I don t think anyone has ever seen an estrogen response I have been trying to find such a case

Dr Kennedy We have a series of premenopausal women who have responded to estrogen It required 1 000 mg of stilbestrol With that dose regressions may occur Dr Nathanson and I had fourteen cases and he referred to this in several articles but the series as yet is not reported We are still adding to it

Dr Ray You got suppression of pituitary function?

Dr Kennedy So I assume I dont know Giving that dose produces amenorrhea Whatever is suppressed the patients condition improves Eye lesions pulmonary lesions and cutaneous lesions have disappeared During the time the dose is being administered if there is trouble getting up to 1 000 mg acceleration of the disease may occur We have two or three patients in whom the disease was accelerated

Dr Matson Should not every premenopausal woman with metastatic cancer be oophorectomized or do you think you should go directly to hypophysectomy?

Chairman Pearson I would think the best way to answer that would be to find out whether or not the premenopausal patient who fails to respond to oophorectomy has a response to hypophysectomy If in a series of twenty or twenty five of these patients all failed to respond to hypophysectomy then I think you can say do oophorectomy first If you find 20 per cent or so of those who failed castration will respond to hypophysectomy then I would think you can go directly to hypophysectomy We have done primary hypophysectomy in six patients that Dr Ray presented Three of these had remissions and it appears that ovarian function is markedly suppressed The vaginal smears and endometrium became atrophic There does not seem to be any measurable function of the ovary in the absence of gonadotrophin I think this is quite an important point and in a group of investigators like this we ought to be able to accumulate twenty five such patients It is possible that some patients will benefit from hypophysectomy who do not benefit from oophorectomy

Dr Rhoads Have you seen responses to hypophysectomy in women who are more than ten years postmenopausal?

Chairman Pearson Yes even twenty five years postmenopausal

Dr Rhoads In your paper Dr Ray you did not distinguish between responses to hypophysectomy in women with a spontaneous menopause and those with induced menopause

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means anything I think you need a much larger series for the per centage to mean anything

Dr Ray Dr Taylor do you know what kind of surgical pro cedure was used in your group of patients? I know Dr VerBrug ghen was doing one type of procedure one day when I was out there in which he took the tuberculum sella off

Dr Taylor That is the patient who was blinded I remember when you were out there Now they are both apparently doing your procedure

Dr Ray They gave up removing the tuberculum sella then as a routine part of the operation?

Dr Taylor VerBrugghen has been chiselling the anterior clinoids

Dr Ray That is something we have not done except in three patients where we were unable to get into the sella safely or ade quately Otherwise we have assiduously avoided taking off any bone because I think it adds materially to the possibility of com plications

Dr Taylor We have encountered complications Of the two deaths one occurred in Dr VerBrugghen s service and one oc curred on the service of Dr Gustafson I cannot tell you whether or not he removed any of the anterior clinoid

Dr Ray One cannot chisel or rongeur bone without the pos sibility of transmitting trauma to the optic nerves or to blood vessels in the region After all the carotid artery is adjacent to the anterior clinoids I am sure that it is a more time consuming pro cedure and I think it carries with it more risk of trauma to impor tant adjacent structures

Dr Matson That is absolutely right I have done it two or three times in these patients and once or twice in other types of cases It lengthens the procedure a great deal The main problem we had was venous bleeding It is easy to crack the bone off and stay out of the sphenoid sinus packing the mucosa ahead of you

Dr Ray A lot of manipulation is required

Dr Matson There is a lot of communication between the cavernous sinuses anteriorly It is easy to get into this when the tuberculum sella is removed

Dr Kennedy It certainly takes only a few minutes to chip off the anterior clinoids

DR RAY We broke that down but the slide looked too compli cated to present There is no difference in the response of the two groups

DR MATSON I wonder if that might not be because some of these elderly people who dont menstruate are still producing estrogen and have cortical stromal hyperplasia

DR KENNEDY How many regressions have you seen in women who are ten years or more past the menopause?

DR RAY Would you say women over 60 would you choose some age like that?

DR KENNEDY That is the age group we are interested in

DR LIPSETT There were eighteen patients in the spontaneous postmenopausal group and a number were over 60 one patient was 72 years old many were ten years postmenopausal We had ten responses in this group of eighteen patients

DR MATSON Am I not correct concerning the Smiths bio assays of urinary estrogens [10] that they have found a significant amount of urinary estrogens in some patients in their seventies ten fifteen twenty years past the menopause and that 80 per cent of those patients have shown cortical hyperplasia?

DR BERGENSTAL Dont forget the adrenals produce estrogens in an unknown amount and it varies a great deal I am sure from individual to individual

CHAIRMAN PEARSON The incidence of remissions from castra tion in postmenopausal patients is about 10 per cent, so why put a patient through a procedure like this when you only have one chance in ten to help them

DR JESSIMAN In your series of about twenty patients you find that castration is helpful in 10 per cent The only reason I bring up this point is that in our series which is much smaller we have found a relatively higher percentage than 10 per cent I would say at the moment about 25 per cent We have done many fewer pa tients than you have

DR TAYLOR Twenty five per cent show regression after ooph orectomy?

DR JESSIMAN In patients 65 years or older

CHAIRMAN PEARSON Of fifteen patients who had a spontaneous menopause thirteen obtained remissions from combined oopho rectomy adrenalectomy I dont think the percentage in this series

active iodine uptake did not decrease at all It remained about 50 per cent as far as I can remember The PBI was six pre and post operatively yet the estrogens had dropped

DR MATSON After nine months she is still one of the best examples of remission

DR RAY She had been castrated?

DR JESSIMAN Yes

DR BAKER That has been of some concern to us You have found the change in estrogens that we cannot find It may be that the zinc method of assay may be doing something to the active compound that we do not pick up in our hydrolysate

DR JESSIMAN That is highly possible

DR BAKER I don t think Engle feels that way but I do The patient changes yet we cannot find any change by our method of estrogen assay

DOCTOR Do you do fluorometry?

DR BAKER The method of estrogen analysis is by fluorogenic phenols and then analysis by countercurrent distribution

DR JESSIMAN How long do you hydrolyze?

DR BAKER We hydrolyze for twenty minutes in the autoclave at fifteen pounds pressure

DR JESSIMAN That is the same as we do We hydrolyze for fifteen minutes

DR BAKER We don t use zinc

DR JESSIMAN We do so only for a certain fraction Routine hydrolysis is for fifteen minutes with acid no zinc In this particu lar patient I was talking about we got a change in the TO frac tion as well as the TZn

DR BAKER Vaginal smears are also a complete loss as far as we have been able to see We have not been able to find any change in vaginal smears before and after castration before and after adrenalectomy and now before and after hypophysectomy They don t seem to vary much

CHAIRMAN PEARSON It is rather amazing that you can t find any change after castration in the vaginal smear Dr Treves would you like to comment about Dr Finkbeiner s studies?

DR TREVES As far as the castration group is concerned Dr Finkbeiner has been able to give us very definite information from examination of the vaginal smear He has been able to predict when the process is reactivated due to the secretion of estrogen affecting the tumor process in the body Changes in the smear

DR RAY That is a little bit different than the procedure of Dr VerBrugghen

DR MATSON We had to do it as Dr Ray said twice when the chiasm was prefixed and there was no room It certainly adds to the difficulty of the operation

DR RAY I think that no two neurosurgeons are doing this exactly the same It would be pointless to insist that an operation had to be standardized but there are good and bad points to some of these procedures

DR BERGENSTAL Have you done bio assays for estrogen in hypophysectomized patients?

DR BAKER No

DR RHOADS Have you isolated estrogens in the urine after hypophysectomy?

DR BAKER The estrogens were not isolated as crystalline material but countercurrent distribution of the urines in the patients whom we believed to be totally hypophysectomized showed no change in any of the estrogen fractions One of the patients who had a successful hypophysectomy died suddenly six months after operation This patient had a full blown clinical myxedema and was not on thyroid medication No cause for death was found at autopsy Serum electrolytes prior to death were completely normal and myxedema was thought to be a possible cause of her sudden death

DR BERGENSTAL You find estrone after oophorectomy and adrenalectomy?

DR BAKER Yes we find no difference in countercurrent distribution of estrogen before or after castration or after adrenalectomy

DR BERGENSTAL You were talking about the possibility of conversion of cortisone to estrogen Do you think that is possible?

DR BAKER We have never been able to find any evidence that conversion of cortisone to estrogen exists either by administration of labeled cortisone to patients or by incubation of human tissue slices with carbon labeled cortisone

DR JESSIMAN You asked about the estrogens We use the Smith bio assay with rats I have studied only one of our hypophysectomized patients the estrogens dropped from a high premenopausal level to unrecordable levels It is difficult to know how to judge these tests for completeness of hypophysectomy because this patient has had one of our best responses yet the radio

DR JESSIMAN I have not done any work on that

DR WEST We have analyzed urines from two hypophysecto mized adrenalectomized castrated women maintained on 50 mg of cortisone daily by mouth and failed to isolate any estrogens

DR RHOADS Only 6 per cent of the administered estrone is recoverable as estrogenic material in the urine There is a big chance of other metabolites of estrone being present They may have an effect on breast cancer even though you cannot measure them

CHAIRMAN PEARSON I think the point that Dr Rhoads brought out may not be a familiar one to everyone This is work that Dr Thomas F Gallagher of our staff did with C^{14} labeled estrone After administration of the material, 60 to 70 per cent of the radio activity was found in the urine but only about 10 per cent of the material could be identified as estradiol estrone or estriol In the countercurrent distribution there are other compounds present which have not been identified The bio assay technique would certainly be interesting to compare with chemical measurements Some estrogen metabolites may not have estrogenic activity and thus would not be detected by bio assay

DR RHOADS Yet they could be active in breast cancer

DR WEST Are you concerned about your urinary estrogen assays using the zinc method for hydrolyzing the urines? This method of hydrolysis appears to convert unknown inactive sub stances which may or may not be true metabolites of estrogens into biologically active estrogens of unknown chemical structure Wouldn t it be better to measure the naturally occurring urinary estrogens?

DR JESSIMAN I really cannot argue as Mrs Smith would argue with you I understand that the substance the Smiths are measuring with the zinc hydrolysis is part of the estriol fraction The zinc hydrolysis they believe converts the metabolites or precursors or whatever you want to call them into estriol. This is what is being measured after the three hour zinc hydrolysis

DR WEST Some investigators would prefer to identify what is put out by the body

DR BAKER Dr Bergenstal you previously reported some changes in estrogen excretion which were measured by bio-assay Then you advanced the opinion that perhaps these data were not accurate

DR BERGENSTAL Those studies I am sure have to be done all

have also been noted following adrenalectomy There have been some studies on hypophysectomy which while they are not con stant are suggestive

DR LIPSETT Of the premenopausal women studied by Dr Finkbeiner three were in the progestational phase of the men strual cycle at hypophysectomy They bled two weeks after sur gery and subsequently the vaginal smears became atrophic as with patients who had *oophorectomy and adrenalectomy* On this basis it would seem that the estrogen suppression is pretty com plete

CHAIRMAN PEARSON Dr West will comment on this a little later He has been measuring estrogens by chemical procedures

DR WEST We are currently measuring urinary estrogens by means of photofluorometry To get accurate results by this method it is first necessary to separate the urinary estrogens from other fluorogenic phenolic substances which are normally present in urine This separation is not easy but can be accomplished by a combination of countercurrent distribution and paper chromatog raphy

DR BERGENSTAL This is the crux of our whole problem prob ably We attempt to get rid of estrogens and we find ourselves with no good methods for measuring them or telling whether or not we are affecting them

DR JESSIMAN I wonder if we are not trying to be too great purists in attempting to differentiate the sort of estrogens we are measuring

I am not trying to defend bio assay All I am saying is that the material I inject into my rats produces changes in the estrus cycle and these changes can be measured pre and post oophorectomy and the levels can be shown to have changed

I cannot be precise as to the exact nature of the substances I am measuring but I can look at the estrogen level I have meas ured in a post castration patient and say "This woman s estrogen levels are rising and I predict that in the event of reactivation of her disease removal of her adrenals may produce a remission of her disease Therefore I remove the adrenals What I have meas ured I believe to be estrogens Following adrenalectomy the estro gen levels as measured by the bio assay method of Smith and Smith [10] have fallen

DR TAYLOR You see no evidence that cortisone is converted to estrogen?

Dr Jessiman I have not done any work on that

Dr West We have analyzed urines from two hypophysecto mized adrenalectomized castrated women maintained on 50 mg of cortisone daily by mouth and failed to isolate any estrogens

Dr Rhoads Only 6 per cent of the administered estrone is recoverable as estrogenic material in the urine There is a big chance of other metabolites of estrone being present They may have an effect on breast cancer even though you cannot measure them

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Dr Rhoads Yet they could be active in breast cancer

Dr West Are you concerned about your urinary estrogen assays using the zinc method for hydrolyzing the urines? This method of hydrolysis appears to convert unknown inactive sub stances which may or may not be true metabolites of estrogens into biologically active estrogens of unknown chemical structure Wouldn t it be better to measure the naturally occurring urinary estrogens?

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Dr West Some investigators would prefer to identify what is put out by the body

Dr Baker *Dr Bergenstal* you previously reported some changes in estrogen excretion which were measured by bio assay Then you advanced the opinion that perhaps these data were not accurate

Dr Bergenstal Those studies I am sure have to be done all

over again They showed a change after castration then a further drop after adrenalectomy to essentially zero However there are still some patients after adrenalectomy and castration who did have still measurable estrogens in the urine

DR JESSIMAN I would like to second that With my method I found that patients excreted estrogens after adrenalectomy and oophorectomy

DR RHOADS What method are you using?

DR BERGENSTAL Uterine weight increase

DR RHOADS So in some instances there is unequivocal evidence of estrogenic activity after oophorectomy and adrenalectomy?

DR BERGENSTAL That is right

DR JESSIMAN One could assume this came from adrenal rests

DR ELIEL *Ovarian rests have been described*

DR TREVES What about the hypophyseal rests? In this hospital 33 accessory adrenal glands were found in 100 consecutive autopsies I think all patients may have accessory glands They may not be noticed at the time of operation This is one of the things that confuses the issue

DR LIPSETT Didn t you mention a paper this morning on reactivation of pituitary remnants? Was there a high incidence of nasal pituitaries?

DR LUFT There are no actual figures in Dr Tonnis paper but his group observed histologically reactivation of the nasal pituitary

CHAIRMAN PEARSON We might mention briefly some studies done by Dr Robert Mellors and Dr John C Hubbard of our pathology staff on the nasopharyngeal pituitary They have removed the nasopharyngeal pituitary at autopsy It is rather small about 1 mm in diameter and about 6 or 8 mm long It seems to be a small cylinder They have been particularly interested in finding this in patients who have survived hypophysectomy for some period to see if they could find any evidence of hyperplasia or mitotic activity To the best of my knowledge to date they have not found any evidence that this gland is increased in size or has become hyperplastic However there are cells which appear to be acidophils basophils and chromophobes and they look entirely like anterior pituitary cells It is also possible apparently to remove the nasopharyngeal pituitary in patients Dr David Leisten has attempted this in one patient but I believe he was

unsuccessful in this patient Dr Leisten has removed this gland in children at the time of tonsillectomy and has become quite proficient at finding it We are hopeful that we can get more information about this If this gland is of importance it would seem possible to remove it surgically at the time of hypophysectomy

Occasionally anterior pituitary cells are inside the sphenoid sinus Thus to remove all such tissue might still be rather difficult Less is known about the incidence of pituitary tissue in the sphenoid sinus but it is present in the nasopharynx in about 90 per cent of patients

II

SURGICAL HYPOPHYSECTOMY IN DIABETIC PATIENTS

DR LUFT

IT is well known that the frequency of vascular complications in juvenile diabetes mellitus has increased This is in part due to the increased life expectancy in these diabetics owing to the introduction of insulin in the treatment We have performed hypophysectomy in an attempt to arrest the progression of such complications Up to June 1955 twenty patients had been subjected to the procedure During the fall of 1955 another two patients were operated on

I shall first describe the initial group of twenty cases They were ten males and ten females aged between twenty and thirty three years At the time of operation the duration of diabetes varied between thirteen and twenty two years and vascular complications had been diagnosed one to seven years earlier Diabetic retinopathy was present in all cases Albuminuria was found in all although in four of them only in traces Doubly refractive lipoid elements were present in the urine of thirteen out of sixteen patients before and/or after hypophysectomy The systolic blood pressure was between 140 and 160 mm Hg in eleven cases and 160 mm or higher in five cases A diastolic pressure between 90 and 99 mm Hg was recorded in ten cases and 100 mm or more in six cases Calcification of the peripheral vessels was observed on x ray examination in eight out of eighteen cases

Fourteen patients were alive after the first postoperative year Of these two died fifteen and nineteen months after operation one during a hypertensive crisis and one from renal insufficiency In both there were advanced vascular complications before the operation and both had unfortunately received desoxycorticosterone acetate (DCA) for many months during the postoperative period

Clinical Results

The therapeutic results in the twelve surviving patients up to July 1955 were as follows

Circulation There was a fall in the systolic blood pressure and a tendency for the diastolic pressure to decrease The heart size decreased in most cases In those cases in which calcification of the peripheral vessels was found before operation such calcification was still present at subsequent follow up examinations No further calcification appeared *In all cases except one* the capillary fragility was normal after the operation

Renal Function A definite decrease in the albuminuria was observed in nearly all cases As to the occurrence of lipoid crystals these were absent in four cases after the operation The effective renal plasma flow as measured by p amino hippurate remained practically unchanged after the operation In contrast the glomerular filtration rate markedly decreased This decrease is most probably due to the ablation of the hypophysis and cannot be regarded as a sign of progression of the renal changes Analogous decreases in the glomerular filtration rate were observed by us after hypophysectomy in patients suffering from breast cancer without demonstrable renal disease

Eyes The visual acuity remained on the whole unchanged after hypophysectomy As to the patients sub-

jective impression of their visual capacity an improvement was reported by seven no change by four, and worsening by one These changes have been roughly assessed by the patient's reading ability In ten cases the eyegrounds were followed regularly and permanent records obtained by color photography In one case a marked progression of the diabetic retinopathy was observed after a short period of improvement the progression started at a time when the patient had an exacerbation of rheumatoid arthritis In the remaining nine cases, no definite signs of progression were observed Decrease in the formation of new vessels was observed in five cases In one case, before operation there was very advanced retinopathy in the right fundus with hemorrhage new vessel formation and proliferation One year later the newly formed vessels had disappeared and exudates and proliferations were markedly diminished This improvement has been maintained to date twenty four months after the operation Similar improvement was also observed in the other eye

We concluded from these data that hypophysectomy in a group of diabetics with advanced vascular disease induced a lowering of the blood pressure that there were no signs of progression of the diabetic renal disease after the operation and that except for occasional retinal hemorrhages, no clear symptoms or signs of progression of the diabetic retinopathy were evident

Eight months have passed since we made this review In the beginning of the fall of 1955 we operated on another two patients with diabetes mellitus with very advanced vascular damage We then decided to wait for at least one year before operating on more patients as we considered the series large enough to permit an evaluation of the prognosis after hypophysectomy

The further experience gained during the last eight months has been both positive and negative I shall summarize it

As far as the *circulation* is concerned nothing new can be added the results reported have not changed

As to *renal function,* we can consider the results promising No deterioration has occurred and none of the surviving patients has shown progression of renal disease One patient in particular had all the signs of progressing renal damage before the operation Now four and a half years later no further progression has taken place the sediment has become nearly normal and no lipoid crystals are seen in it the clearance values have remained stable the albuminuria is less and the blood pressure is lower In another patient who had markedly advanced renal disease with anemia and edema before operation the clinical picture has changed completely and all external signs of severe renal disease are gone

As to the *eyes* we must report unfortunately that this operation does not remove the tendency to retinal hemorrhages Even though these take place less frequently they do occur and such a hemorrhage can destroy the vision There always will be a locus minoris resistentiae i e a place of least resistance in these vessels in spite of any favorable effect of hypophysectomy

DISCUSSION

DR RAY What about the insulin requirements after hypophysectomy?

DR LUFT In our patients insulin requirements have gone down If you take away the cortisone for a couple of weeks the need for insulin drops further If you give cortisone you have to increase the dose

DR FORREST How much?

DR LUFT It depends on the dose of cortisone

DR LIPSETT What is the most severe case you have done as far as regards uremia?

DR LUFT The last patient described had what may be called the nephrotic syndrome with NPN occasionally elevated

DR LIPSETT Do you still feel as you indicated in one of your articles that any further elevation in NPN contraindicates surgery?

DR LUFT We do not operate on uremic or pre uremic patients

DR MATSON I gather at the moment you would not recommend operation for somebody with diabetic retinopathy who is normotensive and has normal renal function?

DR LUFT If our present results are confirmed by further experience I would recommend the operation

DR MATSON You say you concluded probably that the operation did not alter the course of the retinopathy?

DR LUFT It does We have seen in at least five cases how the new formed vessels the real proliferative changes decrease and that they may even disappear after hypophysectomy That is an improvement On the other hand there may remain the small aneurysms and the other vascular changes from which hemorrhages may start You may see a few small aneurysms in the ophthalmoscope but there may be many more that you do not see

DR MATSON Would you feel that you could define or delineate at all the kind of a diabetic case you would recommend for hypophysectomy?

DR LUFT Not yet

DR BAKER After operation are they more sensitive to insulin and require less?

DR LUFT Yes

DR LIPSETT Have you had difficulty with insulin reactions?

DR LUFT We had one postoperative death that might have been caused by insulin hypoglycemia

DR RAY I wonder if retinal aneurysms are a common finding or an unusual one? Your notion is that it is characteristic of the diabetic?

DR LUFT The ophthalmologist says so That is the only thing I can say

DR MATSON Did you say what had happened to the other six patients in the first year? I gathered fourteen of the twenty patients survived a year Did the other six patients die operative deaths or die of diabetes or what?

DR LUFT There were two immediate postoperative deaths A third patient died of cerebral anoxia that might have been due to hypoglycemia One patient died of a septicemia and I cannot remember the other two at the moment

DR RAY What is the oldest patient?

DR LUFT Thirty three

DR RAY The youngest?

DR LUFT Twenty

DR RAY Would you have any comment about patients over 30?

DR LUFT We have had no experience with any other age group we have limited our experience to patients between twenty and about thirty years of age

DR KENNEDY We have done two patients over thirty one is forty two years old and one is forty six The first man had an impairment of PSP excretion and a BUN of 30 mg per cent He was normotensive and had marked vascular changes After the operation the insulin was discontinued There was no progression of the retinopathy in the past year and four months The second patient was operated on about four months ago he was a severe diabetic requiring 60 to 80 units of insulin daily There was a reduction of insulin requirements within four months He has not had a retinal hemorrhage in these four months and up to that time he was having repeated hemorrhages We have selected our cases these two were chosen because they had very marked vascular disease but as yet were not blind Thus we had some practical reason for doing the hypophysectomy

DR MATSON We operated on one diabetic six months ago a man of forty two who was blind in the left eye and had only the lower field of vision remaining in his right eye He has had no

hemorrhages since the operation The vision is perhaps the same as it was preoperatively His insulin requirements have dropped from about 40 units a day preoperatively to 6 to 8 units the amount depends upon how much cortisone he is given He is doing well otherwise and is normotensive more of the time than he was before

Dr Kennedy I would like to add one point to my previous remarks Our first patient was not really hypophysectomized When the diaphragm sella was cut bleeding was encountered A needle was placed in the pituitary fossa in an attempt to aspirate the pituitary This failed The patient went into adrenal and thyroid insufficiency between thirty and sixty days after the procedure About that time *his insulin requirement decreased* and the blood sugar decreased Pituitary insufficiency was apparently induced by the trauma

Dr Matson I wonder if Dr Luft would comment on Dr Olivecrona s operative procedure We had a difficult time with our diabetic patient It is quite a different operative procedure from hypophysectomy in a cancer patient In the diabetic the vessels of the brain are about 90 years old Bleeding is much more profuse The arachnoid is thickened and gray The patient whom we hypophysectomized had numerous seizures from the seventh to the fourteenth day which were very difficult to control as was the water metabolism *All of a sudden he straightened out I was* interested in going back to see that that same course of events apparently had happened in Dr Olivecrona s cases

Dr Luft We have seen seizures in most of our diabetic patients except for the first one we operated on All the other patients have had epileptic seizures starting about five to eight days after the operation In most cases the seizures stopped occurring within one week

Dr Matson You felt there was cerebral edema?

Dr Luft Dr Olivecrona thinks so

Dr Matson We reoperated on our patient and found nothing *Then we read in your paper not to go back and look because you* would not find anything

Dr Luft We reoperated on the first patient and he died a little while later Even in cases in which the x rays showed the peripheral vessels to be normal we observed during operation that the superficial vessels on the brain surface were brittle

Dr Matson I am sure that this should be a factor in whether

or not you are going to consider this operation as a therapeutic procedure in diabetics

DR KENNEDY Nobody has suggested that it is therapeutic in diabetes It will take five years to find out whether or not it is helpful to the patient

DR RAY What is the life expectancy in juvenile diabetes? Isn t there a definite figure on it?

DR KENNEDY It keeps getting longer as the years go on be cause of all the ancillary things such as the antibiotics that are aiding the patients There are no reliable figures

DR MATSON After hypophysectomy did your patients have an increased incidence of incidental infections respiratory or other or more trouble with their feet?

DR LUFT No

DR KENNEDY The patient we described previously—the one in whom we failed to take the pituitary out—had had a two-year history of repeated furunculosis He has not had an episode for over a year after hypophysectomy Certainly he has had less in fection and complications However this might represent only close supervision of a diabetic patient

DR BAKER Can you increase the glomerular filtration rate after hypophysectomy? Is this an effect of inadequate cortisone replacement?

DR LUFT Yes In this connection I would like to report in more detail on one of our cases Before operation the patient had a very low glomerular filtration rate with anemia albuminuria low protein levels in the blood hypertension and now and then an elevated NPN Two years after the operation she has no nephrotic syndrome less albuminuria the protein level in the blood is nor mal and she has normal blood pressure Her filtration rate is now nineteen Despite this she is doing fine

DR RAY Would you consider operating on a child?

DR LUFT I do not think so at the moment

DR ELIEL How do you explain the low cortisone require ments?

DR LUFT They feel better if you give them more We are giving them just enough to keep them in good condition

DR ELIEL Do they have any tendency to go into hypotensive collapse? The breast cancer patients do so on occasion with the very low doses of cortisone

DR LUFT I have not observed this

Dr Matson With regard to cortisone we had one interesting patient that perhaps should be mentioned She was not diabetic or at least she did not know she was a diabetic although perhaps she might have been a mild one After being on prednisone for quite a long period of time for treatment of her breast cancer she developed diabetes and required 20 to 30 units of insulin Since hypophysectomy she has not needed insulin she is seven months postoperative

Chairman Pearson Dr Laurance Kinsell[11] suggested that the decreased amount of cortisone replacement necessary in hypophysectomized diabetics may be due to impairment of renal function They perhaps do not excrete cortisone quite as rapidly I was quite surprised when he indicated that diabetics could be maintained quite well on 15 mg a day

III

PHYSIOLOGICAL EFFECTS OF HYPOPHYSECTOMY

DR MORTIMER B LIPSETT

IN our studies of the hypophysectomized patient we were concerned about the responses of the target glands to this procedure because of the intrinsic interest of the problem as well as the need to determine the completeness of hypophysectomy Urinary gonadotrophins as determined by the mouse uterine weight method have generally disappeared promptly after surgery Occasionally we have noted persistence of low titers of gonadotrophins for several weeks after surgery in patients who subsequently proved to have had complete hypophysectomy

Estrogen Excretion

The vaginal smears have become completely atrophic two weeks following hypophysectomy These smears are quite different from those seen in the average postmenopausal woman and indicate almost complete disappearance of estrogen effect In the six premenopausal women who were hypophysectomized cessation of menses was prompt In only one patient was there a suggestion of the menopausal syndrome (Subsequently we have observed two patients who had typical hot flushes following hypophysectomy)

Thyroid Function

Our studies of thyroid function have been reported they confirm the data presented by Dr Luft The serum

protein bound iodine and the 48 hour thyroid I^{131} uptake reach hypothyroid levels within two weeks The signs and symptoms of hypothyroidism do not appear until at least two months after surgery Occasionally, clinical hypothyroidism was not evident one year after hypophysectomy although chemical hypothyroidism was present throughout this time

The incidence of obesity as the first sign of hypothyroidism has been most impressive in these patients Following this, in order of frequency are dryness of the skin thinning of the hair and lethargy

Sodium Metabolism

Although the control of sodium metabolism by the patient with panhypopituitarism has been discussed in the past no definite data were available We examined this problem in eight hypophysectomized patients by studying their response to salt restriction In all instances these patients were able to reduce the urine sodium as quickly to as low a level as a normal subject The maintenance cortisone that they were receiving was not responsible for the sodium conservation as adrenalectomized patients receiving comparable doses of cortisone are not able to reduce the urine sodium to these low levels The recent demonstration of the independence of aldosterone secretion from pituitary control provides the explanation for this Dr John Luetscher Jr of Stanford University demonstrated a marked rise in the excretion of sodium retaining corticoid in the urine of one of these patients subjected to salt restriction These facts combined with a careful review of the pertinent literature suggest that the hyponatremia often reported as evidence of salt loss is actually a dilution hyponatremia due to fluid retention

Hormone Withdrawal and Replacement

Our group has previously noted the necessity of providing the adrenalectomized patient with cortisone It was therefore of considerable interest to evaluate the response of the hypophysectomized patient to either cortisone or ACTH withdrawal Twenty two patients have been studied following withdrawal of cortisone or ACTH this often being carried out in a gradual fashion All of the patients who had a complete hypophysectomy became ill, often severely so when they were not receiving cortisone This happened sometimes within 36 hours usually in three to five days and in one patient symptoms of adrenal insufficiency were not noted for two months The patients demonstrated the classical signs and symptoms of adrenal insufficiency anorexia nausea weakness asthenia fever and postural hypotension During the period of cortisone or ACTH withdrawal the 17 ketosteroids averaged 3 mg per twenty four hours The urine 17 hydroxysteroid levels reached zero in a smaller group of patients so studied As with the adrenalectomized patients there were no detectable changes in any of the metabolic parameters studied

With respect to the maintenance of these patients after surgery we have been using 10 to 15 mg of prednisone or 37 5 to 50 mg of cortisone daily The compound 9 alpha fluorohydrocortisone has proved to have excessive salt retaining effects for satisfactory maintenance

Dr Matson remarked earlier on the difficulties encountered when hypophysectomy was performed on adrenalectomized patients Our experience has been different as we have had essentially no difficulties with thirteen adrenalectomized patients These patients are handled in the same way with one exception that provision needs to be

made for salt replacement We have also had occasion to follow both adrenalectomized and hypophysectomized patients after subsequent major surgery, and this too has been without incidence As well as the high doses of cortisone given to these patients throughout and after surgery we felt that it was important to give triiodothyronine to the hypophysectomized patients to avoid the extra risk that hypothyroidism entails

Carbohydrate Metabolism

Carbohydrate metabolism after hypophysectomy has not been intensively studied The fasting blood sugar dropped 10 to 15 mg per cent during cortisone withdrawal without resulting in clinical hypoglycemia Insulin tolerance tests were performed in five adrenalectomized patients before and after hypophysectomy The dose of insulin and the cortisone maintenance were the same No significant differences in these tests were seen suggesting that growth hormone did not play a role in this setting

Diabetes Insipidus

Diabetes insipidus was observed in 90 per cent of our patients For our purposes diabetes insipidus has been defined as a decrease in concentrating ability of the kidney related to a probably decreased titer of anti diuretic hormone The urine volume in these patients has varied from 2500 cc a day to six liters a day Replacement therapy is given when the polyuria and polydipsia are uncomfortable to the patient Inhalation of posterior pituitary powders three or four times a day or 3 to 5 units of pitressin tannate in oil intramuscularly every two to three days normally suffices We estimate that half of our patients have needed some therapy

The marked variations in the degree of diabetes insipidus and experimental work reported by Heinbecker and White[12] in 1947 suggested to us that the severity of the diabetes insipidus depended in part upon the amount of the pars nervosa removed at surgery Thus it would be very worthwhile to preserve as much of the stalk as possible

None of the patients with diabetes insipidus has been unable to concentrate his urine after moderate dehydration The response varies considerably probably due to the varying remnants of pars nervosa When cortisone was withdrawn the urine volume decreased This was due to reduced appetite leading to a reduced osmotic load The concurrent change in glomerular filtration rate may also have been significant The osmolality of the urine increased only slightly during this period of reduced urine flow

Completeness of Hypophysectomy

We have attempted to correlate these functional tests with autopsy data In the twenty five autopsies to date two patients were found to have grossly incomplete hypophysectomies These two patients showed no significant change in gonadotrophic titer or thyroid function Another patient had a small remnant of anterior pituitary gland remaining and her urinary gonadotrophins remained positive five months after surgery Curiously enough her thyroid function was severely depressed and myxedema was noted A patient recently autopsied showed a fragment of anterior pituitary estimated at 1 to 2 per cent of the gland This patient had a functionally complete hypophysectomy with absence of gonadotrophins in the urine low protein bound iodine and adrenal crisis after withdrawal of ACTH The question is unanswered as to

whether or not fragments such as I have described can still function

In eleven instances the sella turcica was decalcified and serial sections examined In nine of these cases no cells of anterior pituitary origin could be found In the other two, there were rare microscopic clumps of cells Both of these patients had functionally complete hypophysectomies Because the hypophysectomies have generally been complete, we cannot make any statement about the correlation of functional tests with the amount of remaining tissue It would appear that small fragments although anatomically present may not have measurable function

DR. ELIEL

I want to say a few words about a study that has been made on polysaccharides or glycoproteins in patients with advanced breast carcinoma who have been subjected to hypophysectomy This is the work of Dr Marvin R Shetlan at the Oklahoma City Veterans Hospital

Serum Glycoprotein Tests

The serum glycoproteins are simply carbohydrates in combination with alpha 2 globulin as identified by electrophoretic mobility The test for determining them is extremely simple One merely precipitates the protein releases the carbohydrate by acid hydrolysis and does a simple photospectrometric measurement of the supernatant which determines the glycoprotein content The normal range is from 1 5 to 2 per cent of total serum proteins Any value in excess of 2 per cent is considered abnormal There are sufficient data to establish the fact that the levels above two are definitely abnormal Serum glycoproteins are uniformly elevated in patients with malignant neoplasms and are not elevated in benign neoplasms It is non specific in the sense that one finds the level occasionally elevated in infections in tuberculosis and in rheumatoid arthritis It is of interest that it does subside to normal levels when there has been adequate definitive therapy for malignant neoplasms

I would like to suggest that this test might serve as an objective though crude criterion of tumor growth rate to be used in patients who do not have elevated urine calcium excretions

For example Table 13 shows data from a patient (L E) who did not get a remission following hypophysectomy I described this case in some detail this morning The

serum glycoproteins prior to hypophysectomy were definitely abnormal, above two A typical rise followed immediately after surgery and subsided again to preopera

TABLE 13

Serum Glycoproteins

L E	Rx	PR%
7/ 5/55	Pre hypox	3 09
7/14/55	Pre hypox	2 95
7/21/55	Post hypox	3 65
7/28/55	Post hypox	3 48
8/16/55	Post hypox	3 21
8/30/55	Post hypox	3 30
12/ 2/55	Post hypox	3 66
	No remission	

tive levels The level rose terminally as the patient s disease became more extensive

Table 14 shows data from two more patients One

TABLE 14

Serum Glycoproteins

L W	Rx	PR%
1/11/56	Pre hypox	2 42
3/13/56	Post hypox	2 30
	Partial remission	
A A		
1/24/56	Pre hypox	2 43
3/13/56	Post hypox	2 46
	No remission	

(L W) showed partial arrest of her disease without much change in the serum glycoprotein content after post hypophysectomy The second patient (A A) who failed to get a remission similarly showed no change

Table 15 shows data on the patient who was the first one listed on Table 12 presented previously (page 42)

She obtained an excellent remission following hypophy sectomy She had an abnormally high glycoprotein level preoperatively which after hypophysectomy came down within the normal range She had repair of osteolytic

TABLE 15

Serum Glycoproteins

V T	*Rx*	*PR%*
9/ 7/55	Pre hypox	2 67
1/10/56	Post hypox	1 98
3/13/56	Post hypox	1 73
Remission Repair osteolytic metastases Complete resolution pleural effusion		

metastases in the spine and complete resolution of a massive left pleural effusion Whether or not this test will be as sensitive or rapid in its changes as the urine calcium is when a good remission is induced we cannot say yet

Glucose Utilization

The second part of the presentation deals with studies of glucose utilization in patients with advanced breast carcinoma who have been subjected to hypophysectomy This work was carried out by Dr A J Alvarez The test of glucose utilization that we have used is that devised by Amatuzio [8] with the patient in the fasting state 25 gm of glucose are injected intravenously in 50 per cent solution over a time period and eleven blood samples are taken at intervals up to about 1 5 hours after infusion The results of this test I believe are reliable and fairly reproducible as long as they are done under constant conditions such as can be obtained on a metabolic ward The glucose levels measured after infusion are expressed as an increment over the fasting level and are plotted on

semi log paper One then gets the rate of disappearance of glucose from the blood which is expressed as per cent disappearance per minute The normal rate of glucose utilization is thought to be in the neighborhood of around 2 per cent to 3 5 per cent or so Levels below 2 are generally found in diabetics and levels above 3 5 should probably be considered as abnormally high rates of glucose utilization The glucose disappearance rate is merely a net rate determined by rates of utilization, gluconeogenesis and excretion This test is probably of greater significance when values are compared in the same individual than when different subjects are compared

TABLE 16

Glucose Utilization

V T ♀ 42	Rx	K%
9/13/55	Pre hypox	2 6
9/21/55	Pre hypox.	2 1
10/21/55	3 wks p o no steroid	5 1
11/10/55	Cortisone 75 mg/day	3 9
Complete hypophysectomy remission 5 months		

Table 16 shows glucose utilization in a patient who obtained complete remission following hypophysectomy Before hypophysectomy her glucose utilization rates were normal on two tests Three weeks postoperatively when steroids were withdrawn to test the completeness of hypophysectomy the glucose utilization rate went up to a high level 5 1 This patient was completely hypophysectomized by physiologic criteria and went into collapse on withdrawal of steroids With maintenance doses of cortisone she had a somewhat lower level of glucose utilization which approximated normal values There is certain

ly a suggestion from this test that one has a means of testing the integrity of the pituitary adrenal axis as far as ACTH is concerned

Table 17 shows glucose utilization data from a patient (A A) who had mild diabetes preoperatively She had an elevated fasting glucose level preoperatively and occa

TABLE 17

Glucose Utilization

A A ♀ 49	Rx	K%
1/20/56	Pre hypox	1 5
1/24/56	Pre hypox	2 2
	Post hypox	
3/ 6/56	Cortisone 50 mg/day	3 2
3/ 8/56	Cortisone 50 mg/day	3 0
3/16/56	No steroid	5 0
Mild diabetes pre-op None post-op Complete hypox No remission		

sionally spilled sugar in her urine She did not require insulin Two glucose utilization levels were determined preoperatively one was definitely in the diabetic range (1 5 per cent per minute) and the other was low normal (2 2 per cent per minute) After hypophysectomy when she was taken off the steroids for testing completeness of hypophysectomy (which was established by physiologic criteria) the value was very high (5 per cent per minute) showing a rapid rate of utilization While she was getting 50 mg of cortisone the values were both in the normal range (3 0 to 3 2 per cent per minute) It would appear that a high utilization rate is a concomitant of complete hypophysectomy in the absence of replacement therapy

Table 18 is from a patient (L W) who was incomplete

ly hypophysectomized She continued to show FSH in her urine following hypophysectomy The I^{131} uptake remained around 30 to 40 per cent at twenty four hours and the serum protein bound iodine remained above 5 micrograms per cent The pre and post hypophysectomy utilization values are in the normal range and there was

TABLE 18

Glucose Utilization

L W ♀ *46*	*Rx*	*K%*
1/ 5/56	Pre hypox	2 6
1/10/56	Pre hypox	2 3
	Post hypox	
2/13/56	9 fluoro F 0 6 mg	2 9
2/22/56	9 fluoro F 1 0 mg	3 5
	Hydrocortisone 20 mg	
2/28/56	Hydrocortisone 40 mg	2 0
3/16/56	None	2 2
Incomplete hypox partial remission		

no change when steroids were omitted from her regimen which would confirm the fact that the pituitary was probably functionally intact Of interest, however is the fact that her rates of utilization when she was on 9 alpha fluorohydrocortisone were higher than either of the values when she was not receiving steroids I cannot say whether these values are significant because these are the only data that we have It does suggest the very interesting possibility that 9 alpha fluorohydrocortisone suppresses pituitary function without actually interfering with glucose utilization or oxidation This will certainly require confirmation On the other hand when the patient was receiving moderate doses of hydrocortisone the utilization values were essentially the same as the pre and post operative values

Sodium Metabolism

Figure 1 illustrates one of the points that Dr Lipsett brought up that is, that patients who are maintained on pitressin sometimes develop hyponatremia This is our only patient in whom we have observed this phenomenon

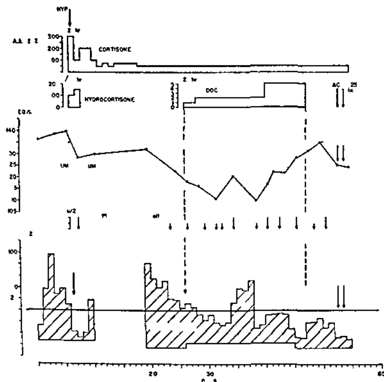


FIGURE 1

but the degree of hyponatremia which was observed here was rather extreme We have the sodium balance plotted in conventional fashion Doses of pitressin are indicated by arrows it was given when the hourly urine volumes exceeded 150 cc Serum sodium levels here and steroid

therapy are plotted There was a brief period of diabetes insipidus after hypophysectomy at this point which was followed by a period of some ten or twelve days when urine volumes were normal The sodium loss during this period may represent a diuresis following the high initial doses of steroid given I do not believe it represents sodium loss resulting from the hypophysectomy It is interesting to note however that as soon as pitressin was given serum sodium concentration levels fell very rapidly At one point it was 118 mEq/L and we began administration of desoxycorticosterone If our analyses had been a little more current we would have waited but we were not aware of the rapid change in the sodium excretion levels At any rate it is of interest that when the DOCA dosage got up to 2 mg per day, and finally to 5 mg, there was a very definite rise in the serum sodium level to normal and that when the DOCA was stopped there was again an immediate fall Coincident with this rise and fall there were changes in the water balance which would suggest that at least part of this rise was accomplished by elimination of water from extracellular fluid I am sorry I have not plotted the water balance data but they were not available when this chart was made That these changes (i e hyponatremia) were not due to primary adrenal cortical insufficiency I think is demonstrated clearly by the ACTH test—25 units intravenously on each of two days—which cut the urine sodium excretion in half and doubled the 17 hydroxycorticoid excretion I think the integrity of the adrenal cortex was established by this test The study does suggest that desoxycorticosterone under these conditions will promote a water diuresis and also that this effect may be mediated at the level of the renal tubule rather than through the pituitary

Of twenty two patients hypophysectomized thirteen had an immediate postoperative polyuria lasting beyond the first day Of these nine continued as a permanent diabetes insipidus A total of seventeen patients eventu ally developed permanent diabetes insipidus which ap peared five days or more postoperatively One patient re verted to normal at the end of five months this cannot be correlated with any other metabolic evidence of regen eration of the pituitary or with any exacerbation of the disease Ten patients received pitressin Two of these dis continued the pitressin because it was more bother than drinking the extra quart of water a day

Endocrine Function

Our studies are similar to others Most of the patients have had low ketosteroid excretion less than 5 mg A rise occurs in the postoperative period because of the high dose of cortisone The ketosteroids have been of little value as a test of adrenal function

We encountered an interesting problem of thyroid func tion A woman in her forties who had been oophorecto mized one year previously had extensive bone metastases There was no clinical evidence of thyrotoxicosis and the serum protein bound iodine was normal She was given 250 mg daily of prednisone for a period of thirty days During this period the protein bound iodine increased steadily to 12 3 gamma per cent the BMR was +26 and the I^{131} uptake 50 per cent There was no evidence of thyrotoxicosis The pulse was relatively normal At the end of the prednisone therapy there was a typical moon facies We could not explain the laboratory findings Hypophysectomy was performed which she tolerated ex tremely well In a study made three months postopera

tively, the protein bound iodine was normal the BMR decreased to -35, the iodine uptake was 8 per cent There was clinical evidence of myxedema with weight gain dry skin constipation fatigue, and slow reflexes I do not know whether we induced subclinical thyrotoxicosis with prednisone therapy or if this was just a coincidental change in the patient

DISCUSSION

DR TAYLOR Dr Lipsett you stated that your patients demonstrated classic signs of adrenal insufficiency when cortisone was withdrawn Is it possible that this is not necessarily proof of complete hypophysectomy but perhaps only a response to sudden cortisone withdrawal?

DR LIPSETT We realize this is a valid objection In a considerable number of patients maintained on ACTH however we have gradually stopped ACTH and seen the same phenomenon This might answer that objection

CHAIRMAN PEARSON Also in the patient with intact adrenals if you withdraw cortisone the blood corticoids can drop to zero at something like forty eight hours but they return to normal levels again at seventy two hours The patient has a period of marked adrenal insufficiency but soon recovers

DR TAYLOR Within thirty six hours?

CHAIRMAN PEARSON In four or five days When cortisone is stopped abruptly in rheumatoid arthritics for example who have been kept on cortisone for years the blood corticoids will show this very transient fall but they will recover spontaneously

DR TAYLOR What value do you think ACTH stimulation has in assessing pituitary function?

DR WEST We have been using the Bliss ACTH test[14] for adrenal function This consists of the administration of 25 units of ACTH intravenously over a two hour period measuring blood corticoids before and after In patients who have been hypophysectomized for a number of months we find no response to this However if we put these patients on intramuscular ACTH for three or four days we can show that the blood corticoids begin to rise and then the patient becomes responsive to the Bliss test The initial lack of response to ACTH may be due to adrenal atrophy

DR FORREST These findings of Dr West s agree with the failure of ACTH to decrease the eosinophils in Dr Luft s cases

DR KENNEDY For your patients with diabetes insipidus do you use tannate or nasal insufflation?

DR LIPSETT In some the posterior pituitary powder does not work Some patients get inflammation of the nasal mucous membranes Those patients get the tannate

DR LUFT Do you think the cauterization of the stalk can have anything to do with the development of diabetes insipidus?

DR LIPSETT The pars nervosa contains cells and neurons The more of these you remove the greater the degree of diabetes in sipidus If you coagulate the stalk at the critical level for the development of diabetes insipidus the greater the damage to the stalk and the greater the diabetes insipidus

DR LUFT As far as I can remember we had to give pitressin for a long period of time to only two patients They had invasion of the hypothalamus by carcinoma

DR LIPSETT Dr Luft were your patients eating well when the urine volume was low? The volume depends in large part on the osmotic load and if they are feeling better and eat more the urine flow goes up

DR LUFT They were eating all right

DR MATSON What fluid levels are you willing for patients to maintain without pitressin turning over two four or six liters a day?

DR LUFT They may have an increased urinary output for some months from two to four liters per day while on 25 mg of corti sone per day

DR MATSON Can they sleep through the night without getting up?

DR LUFT I presume they have to get up once a night maybe twice

DR TAYLOR Don t you find you have more polyuria in patients given 50 mg of cortisone daily? We find patients who have not been adrenalectomized put out more urine when given 50 to 75 mg of cortisone

DR LIPSETT I think more of our patients are on 37 5 mg of cortisone or 15 mg of prednisone In these patients the polyuria may still be considerable I think it is a very rare patient who does not have to get up at least once during the night a number of them several times during the night

DR TAYLOR They do on cortisone alone even when they are not adrenalectomized or hypophysectomized

DR LIPSETT Large doses have been reported to cause poly uria I don t think maintenance doses of 37 5 mg of cortisone or 15 mg of prednisone do

DR TAYLOR I wonder if we should use 50 mg of cortisone for maintenance I feel despite the fact that patients don t feel well unless you keep them up to that level that we are giving more

than a physiologic dose because most of these patients have some rounding of the facies and may show a little hypercorticism

Dr Jessiman We were very interested in this problem particularly after reading Dr Luft s paper in which he reduced the maintenance dose of cortisone to 25 mg a day or lower We attempted to do this and noted two things First, although the dose could be reduced to 25 mg the patients did not do well They were anorexic nauseated and could not leave bed—they appeared to be on the verge of an Addisonian crisis Second once reduced to this level these patients had pitressin requirements that were just as great as they ever had been

Dr Taylor I was thinking more about the adrenalectomized patients You keep them on 50 mg of cortisone over a period of a year or more They get too fat, most of them It is hard to keep them down to normal weight The facies get a little rounded and I get the impression that they are not receiving physiologic doses of cortisone yet they cannot carry on their full duties as housewives and so forth without keeping the dose at that level sometimes 62 5 mg if they are doing a lot of work

Chairman Pearson I think the point that Dr Lipsett was making was that as far as the diabetes insipidus is concerned 25 50 or 75 mg of cortisone do not affect this unless it affects the amount of food the patient eats In other words this is all dependent upon the osmolar load in the diet

Dr Luft When we put our patients on a low osmotic load the urine volume decreased markedly May I ask Dr Lipsett if his patients need pitressin later on even after the sixth postoperative month?

Dr Lipsett The patients who needed pitressin still need it We have not studied this systematically however that is by urine concentration or thirst tests many months after hypophysectomy

When I state that diabetes insipidus varies in severity what I mean is that the patients will show an increase in the osmotic concentration of urine after ten hours of fluid deprivation It is not as high as the normal patient but they are able to concentrate satisfactorily up to a specific gravity of 1008 to 1014 Diabetes insipidus is never as complete as in idiopathic diabetes insipidus where the specific gravity is 1005 This is rather a hard topic to study In patients with diabetes insipidus if you withdraw the cortisone you simultaneously reduce glomerular filtration rate

You reduce appetite and osmotic load and the changes in urine flow which you see are easily explainable on the basis of decreased glomerular filtration rate and decreased osmotic load resulting from withdrawal of the cortisone

In one study for instance of a hypophysectomized patient in whom cortisone was withdrawn the urinary flow decreased to approximately 1500 cc per twenty four hours so that on the basis of urine flow alone you would not say the patient had diabetes insipidus The glomerular filtration rate also fell With anorexia the solute intake also fell so that the load was less The change in urine concentration in milliosmols per liter of urine is rather in significant It rose from 150 milliosmols to about 210 With dehy dration the patient could reach 230 milliosmols per liter so it could not be said that the diabetes insipidus improved in this pa tient because the cortisone was withdrawn The polyuria decreased but the diabetes insipidus and the concentrating ability of the kidney remained approximately unchanged

Dr Luft in the paper that Dr Ikkos[13] presented from your laboratory did he state that the thirst tests in your patients showed that the patients could not concentrate urine?

Dr Luft That was during the first two months They can concentrate later on

Dr Lipsett Some of these patients can concentrate somewhat in the first two months when maintained on maintenance corti sone if you dehydrate them there is a reasonably marked rise in the specific gravity of the urine

Dr Luft I do not want to leave you with the impression that our patients have normal water balance Our patients do not react promptly to a water load they cannot dilute in normal fashion

Dr Forrest It comes out in the afternoon if you give it in the morning?

Dr Luft Yes

Dr Lipsett If they are receiving adequate amounts of corti coids meaning 50 to 62 5 mg of cortisone daily it is our impres sion that they react normally to a water load

Dr Luft There still seems to be a difference between our groups of patients Our patients don t need pitressin on 25 mg of cortisone There is another difference our patients can be main tained satisfactorily on 25 mg of cortisone per day

Dr Lipsett There may be a difference in the surgical tech nique

Dr Luft I think Dr Olivecrona cuts the stalk at any level that he reaches during the operation These patients can produce pitressin after the operation We have tried the nicotine test on a few of them and in all of these we achieved a reduction of urine flow and an increase in specific gravity

Dr Lipsett They all have remaining pars nervosa tissue It would appear from the animal studies done by Heinbecker and White[12] that at some point in sectioning the stalk we get diabetes insipidus There is a critical level and we should try to get as low on the stalk as possible

Dr Matson I wish you would find some way to stain the stalk differentially so that the critical area would be apparent.

Four of our patients have been tested with hypertonic saline and with nicotine These patients had stalk section without clip ping or cautery and these four have shown a capacity to secrete antidiuretic hormone In three other patients who have severe dia betes insipidus and who had the stalks clipped and cut neither by nicotine nor sodium chloride have they shown evidence of anti diuretic hormone activity at all. I would guess these are two three or four months postoperative they are all still getting pitressin tannate in oil at home

Dr Lipsett I want to make one more comment to get Dr Luft s reaction We have not made a systematic study of the changes in glomerular filtration rate before and after hypophysec tomy In five or six cases in which we used inulin clearances and creatinine clearances there were only minor changes after hy pophysectomy with the patient maintained on cortisone The reason I bring this up is that we did not see anything like the mag nitude of change in glomerular filtration rate that has been seen in the dog by the group at Bellevue[16] and I know you stated that the glomerular filtration rate fell in many of your patients The cortisone dosage is however considerably lower This may be the difference

Dr Luft As I mentioned before we have not studied our patients on different doses of cortisone That remains to be done

Dr Bergenstal We have found some of our patients needed pitressin and some have not They still are not able to respond to a solute load properly They do have some concentrating ability but with wide variations

Dr Forrest Several of our patients who have diabetes in

sipidus complain that their thirst and polyuria is greatly increased if they take extra cortisone Conversely stopping the cortisone may reduce the fluid intake and urinary volume to normal levels although admittedly this is not in metabolic balance In two patients on balance studies the substitution of prednisone for cortisone did not affect the diabetes insipidus although one patient on 10 mg per day lost salt

DR LIPSETT We have not observed salt loss in seven patients we studied on sodium balance I have one case that I wanted to mention a patient who after two months without cortisone did not appear Addisonian She did however become hypothyroid We were rather convinced that hypophysectomy was incomplete because of this She was put on two grains of thyroid daily which is our usual substitution dosage Two weeks later there was a drop in blood pressure and nausea and vomiting We gave her 37 5 mg of cortisone and there was a very prompt response In this patient, unfortunately we did not have the ketosteroid determinations We assumed it was an incomplete hypophysectomy At autopsy she was proved to have a complete hypophysectomy So I can say this probably represents an extreme variation in survival after complete hypophysectomy without cortisone replacement

Dr Eliel I would like to know if you encountered difficulty administering glucose to patients in cortisone withdrawal?

DR ELIEL No we did not

DR BAKER Don t cancer patients have a high diabetic type glucose utilization or is it normal?

DR ELIEL No our patients have generally been in the normal range

DR BERGENSTAL Dr Eliel the only thing I am wondering about in the study shown on your chart is the lack of constancy of pitressin injection this variability may well account for some of the changes you are getting

DR JESSIMAN That is a good point One of our patients was given frequent doses of pitressin This produced water retention and the serum sodium fell to 114 mEq/L We stopped the pitressin and the serum sodium rose to 140 mEq/L without any other therapy

DR ELIEL That may possibly be true The doses were purposely kept small because of the fact that this patient had hypercalciuria We were unwilling to induce oliguria and renal cal

cinosis I think your point is valid and the study would have been more significant had pitressin been given regularly It does suggest nevertheless that desoxycorticosterone has some effect on water excretion and this would in fact tend to confirm some of the previous work of Gaunt which demonstrated that desoxycorticosterone produces water diuresis in water loaded animals

DR MATSON May I ask Dr Luft a question? Did you say that several patients who had remissions of eighteen to twenty two months were found to have incomplete hypophysectomies at autopsy?

DR LUFT I mentioned two patients who must have had incomplete hypophysectomies according to the results of some function tests Despite this they showed regression of the tumor

DR MATSON They had thyroid function left as determined by the protein bound iodine and radioactive iodine uptake? These patients had prolonged clinical improvement?

DR LUFT Yes

DR MATSON What about post mortem findings? Were there any patients who had twenty month regressions who still had gland in the sella?

DR LUFT I cannot comment on that yet

DR JESSIMAN This morning you said that you operated on four patients who had had a previous oophorectomy and adrenalectomy and three died who had apparently advanced disease What happened to the fourth?

DR LUFT She was operated on three weeks ago and is living

DR RAY I am surprised that Dr Luft has not observed any postoperative convulsions because any surgical exposure and manipulation of the brain may lead to convulsions We believe one or two patients had unrecognized metastases in the motor areas there is that possibility to be considered also I dont think there is anything particularly remarkable about convulsions occurring occasionally after craniotomy performed for whatever purpose

DR MATSON I had one patient in whom there were two visible metastases in the frontal lobe We took the more accessible one out and left the other one in She has had no seizures since operation She has been in remission now for six months

DR ELIEL It might be worth mentioning two experiences we had with convulsions which were induced during the preoperative preparation The patients were given 100 mg of cortisone intra

muscularly and each developed a generalized Jacksonian convulsion Both subsequently turned out to have cerebral metastases The operations were postponed because of the convulsive episodes Both of these patients also had hypercalcemia and hypercalciuria The serum magnesiums were low Rubin[17] has described a reciprocal relationship between calcium and magnesium When the calcium is high the serum magnesium tends to be low We have wondered whether the combination of cortisone and hypercalcemia with or without lowered magnesium levels may not have triggered the convulsive episodes

DR TAYLOR We have a series of patients with cerebral metastases many of whom had convulsions When they were given *100* mg of prednisone per day the convulsions stopped and there was disappearance of the neurological abnormalities within twenty four hours We now have about eighteen patients with cerebral metastases whose neurological abnormalities disappeared with prednisone therapy

CHAIRMAN PEARSON One question of importance is whether or not the pituitary hormones per se have any effect on breast cancer There has been some suggestion of this and I wonder if anybody has any further data with growth hormone or prolactin

DR JESSIMAN We have duplicated your classic experiment of giving growth hormone to a person with osseous metastases who had gonadectomy and hypophysectomy and was in a period of remission As soon as we gave growth hormone there was clinical evidence of exacerbation of the disease and a rise in urine calcium falling to within normal levels after a few days

DR BERGENSTAL What dose?

DR JESSIMAN 100 mg a day on two consecutive days intravenously

CHAIRMAN PEARSON We have one other castrated adrenalectomized and hypophysectomized patient who had a transient remission and was given growth hormone We observed a rise in calcium excretion The growth hormone was stopped and the calcium excretion decreased However her disease exacerbated again within a short time after this study We have given prolactin to one patient who was castrated and had obtained a two month remission from hypophysectomy She was given 100 mg of prolactin daily for eighteen days There was a very prompt rise in calcium excretion in the urine which went up stepwise and hypercalcemia

developed after eighteen days When the prolactin was stopped hypercalcemia and hypercalciuria persisted and she died five weeks later of progression of disease We are unable to determine whether the prolactin did exacerbate her disease or whether the disease was about to relapse spontaneously at the time prolactin was given

Dr Eliel Is your prolactin free of other pituitary hormones?

Chairman Pearson This prolactin was prepared by Dr C H Li of the University of California He told us that this preparation was essentially free of other pituitary hormones

Dr Taylor Is your growth hormone contaminated with TSH?

Chairman Pearson We have not been able to detect any thyroid stimulating hormone in the doses we used as measured by the patient s iodine uptake and protein bound iodine

Dr Taylor We gave growth hormone for twelve days to one patient who had been oophorectomized adrenalectomized and hypophysectomized The patient had a marked exacerbation of bone pain While on the growth hormone the protein bound iodine was elevated and she had signs of thyrotoxicosis Our growth hormone appeared to be contaminated with TSH

Chairman Pearson Dr Kennedy have you had any experience with growth hormone in breast cancer patients?

Dr Kennedy I have only given it to two prostatic cancer patients Both had previously been orchiectomized and had received estrogen Both had exacerbation of the disease and aggravation of pain Therapy could not be continued for more than six days From being mobile walking around the wards they became bedridden The acid phosphatase increased in one from 13 to 19 Bodansky units in six days The urinary calcium excretion increased from 150 mg to 280 mg a day It certainly appeared that these two patients were made worse and we felt this was due to the growth hormone

I was trying to do the same type of study Dr Joseph C Aub and Dr Ira T Nathanson had done with testosterone In patients with prostate cancer one injection of testosterone may produce a marked exacerbation of bone pain Presumably it is due to stimulation of tumor growth and may be associated with a rise in serum acid phosphatase

Dr Baker Patients with acromegaly may have increased calcium excretion Four of 10 acromegalics had evidence of over

activity of the thyroid and urinary calcium excretion of over 200 mg per day

DR TAYLOR On the basis of the thyroid?

DR BAKER You could not be sure They had overactivity of the thyroid but the supposition was that it was growth hormone

CHAIRMAN PEARSON That raises some question as to whether or not growth hormone might induce hypercalciuria in normal sub jects We have given growth hormone to six patients with chronic lymphatic leukemia who appeared to have normal bones There was no significant change in the urinary calcium excretion The calcium balance remained essentially the same Dr Ephraim Shorr[16] reported some retention of calcium in a few patients who were given growth hormone

DR JESSIMAN We have given growth hormone to three other patients with osseous metastases from carcinoma of the breast In none of these patients have we seen a rise in calcium but each one of them has shown a marked systemic reaction increase in malaise bone pain and so on In contrast to this we have made metabolic studies on patients who did not have cancer These patients when given growth hormone have not shown a systemic reaction We have felt that perhaps this is a systemic reaction of the disease to the hormone in the same way as we see a systemic reaction to the administration of stilbestrol in patients with a "hormone stimulated" tumor and osseous metastases

DR BAKER There is some evidence that growth hormone may be species specific which may account for the lack of the expected metabolic effects of beef growth hormone in human subjects

CHAIRMAN PEARSON It certainly has been very difficult to dem onstrate any other physiologic effects with beef pituitary growth hormone in man and the changes that have taken place have been minor nothing like you might anticipate It does raise the question concerning specificity

DR LIPSETT I would like to ask the group if in any of the patients who failed to respond to hypophysectomy or responded and then relapsed was further therapy worthwhile?

DR KENNEDY We have had two patients who responded to androgen and four that did not respond to estrogen

DR LUFT We tried androgen in five or six cases and had no response

DR LIPSETT We have not seen any objective response to andro gen or estrogen after hypophysectomy

Dr Forrest Are there any figures on the number of patients who responded to hypophysectomy and later relapsed due to re turning function of the pituitary? Are there patients who failed to respond to a complete removal? This seems to be a very crucial question

Chairman Pearson In our series we have not been able to demonstrate a returning of pituitary function in association with relapse of the disease One patient who failed to respond to incom plete hypophysectomy also failed to improve after complete re moval of the pituitary

Dr Baker I would like to hear some comments on red cell studies after hypophysectomy whether or not any patients devel oped so-called hypophysis type of anemia which investigators such as Robert Crafts[19] have observed in animals If the anemia did occur to what did it respond? We have the other parameter myxedema type anemia which also may be occurring in these pa tients I just wondered if any studies had been done on red cells or on red cell survival before and after hypophysectomy

Dr Lipsett We have not studied the problem systematically A number of patients maintain normal peripheral counts and nor mal reticulocyte counts many months after hypophysectomy There were two patients who at nine months and a year respectively following hypophysectomy had normal circulating red cell masses With these criteria we could miss a small change say of the order of 10 per cent or 15 per cent but nothing very gross Those pa tients are maintained only on thyroid and cortisone so there is certainly no evidence for any large effect of growth hormone on hematopoiesis in humans There may be a small effect which we might possibly pick up with finer techniques

Dr Kennedy We have been interested in the matter of the relationship because of the earlier studies on the effect of andro gens in the red cell formation You are aware of the sexual differ ence in the hemoglobin and red counts in the male and female the male always running a little higher Administering androgen to patients with metastatic breast cancer produces elevations in hemoglobin even to the state of polycythemia This is a definite erythropoietic stimulation It is very important that the andro genic hormone is an agent of this sort There are not many eryth ropoietic agents that are specific stimulators which can cause the red count to go higher than the normal range In our two male diabetic patients there has been a very striking decrease in the

red cell mass and the hemoglobin in both cases fell to 10 to 11 grams This is in the same range as was originally reported in eunuchs by McCullagh[20] about fifteen years ago The low hemoglobin is corrected with androgenic hormone Both these patients received testosterone One was treated too recently to evaluate but the first patient who had been hypophysectomized nine months previously recovered when placed on testosterone His hemoglobin increased from 10 5 grams to almost 15 grams within a period of *five months In this* one patient we have corrected the anemia which would appear to be the hypophysectomy anemia that so many people have reported in animals This anemia probably is due to lack of androgenic hormone rather than to loss of a pituitary hematopoietic factor You might expect the anemia to occur in women following hypophysectomy since the adrenal androgen is gone but we have not noticed this to any degree

Dr Matson We have not been bothered with anemia in the females but the one male patient with carcinoma of the breast whom we hypophysectomized was extremely anemic He had quite a few transfusions

Dr Kennedy I noticed last year that Dr Kinsell[11] in his report on diabetics pointed out that following hypophysectomy the hemoglobin in his patients rose He was also giving these patients methyltestosterone as a supplement I am sure the hemoglobin rise he observed was due to the methyltestosterone

We have been interested in treating patients who have other anemias with testosterone The anemia of a patient with myelofibrosis with the peripheral picture of chronic myeloid leukemia did not respond to myleran therapy The hemoglobin was 5 grams For ten months he has been given testosterone The hemoglobin is now 14 grams The marrow now is a hypercellular hyperplastic normoblastic marrow It is a very striking change It would appear that the red cell production has been stimulated by the testosterone

Doctor We have tried the 17 ethyl 19 nor testosterone Given by mouth it had little effect on the cancer but the hemoglobin level rose

Dr Kennedy *Regardless of their effect on cancer of the breast* all the virilizing androgens appear to have a hematopoietic effect

Dr Baker We have had a similar experience We have studied red cell mass using radioactive chromium phosphate and find the patients receiving potent androgens have polycythemia which by

our test is indistinguishable from polycythemia vera In one patient there is a significant uptake of Fe^{59} in bone marrow as measured by surface count suggesting that we are stimulating the hematopoietic tissue All ten patients had adequate blood volume before the red cells increased This effect has not been seen with estrogens although in some cases the hemoglobin increased in patients on cortisone We have observed the same increase in blood volume after cortisone therapy although we have not done the Fe^{59} studies in these patients

DR KENNEDY Those patients have an androgen source

DR KENNEDY This phenomenon does not occur in our experience when there is an iron deficiency Obviously you cannot make red cells and hemoglobin without the iron Those patients who have a serum iron below the normal range will have a normoblastic hyperplasia of the bone marrow but the peripheral red count will not increase Neither will the red cell mass until iron is administered to correct the iron deficiency Then there is a quick rise in peripheral hemoglobin red cell mass and hematocrit

DR BAKER Incidentally there is increased red cell survival in addition to more active hematopoiesis under androgen therapy Red cell survival is decreased before androgen administration and after administration it returns to a more normal survival pattern

DR KENNEDY It is not increased above normal is it?

DR BAKER No not above

DR KENNEDY Some of your patients may have in part the hemolytic type anemia do they not?

DR BAKER You have to call it a hemolytic type anemia

DR KENNEDY Our patients had normal red cell survivals before androgen therapy and demonstrated no changes in survival after androgen was administered We thought this important to define exactly where the testosterone is exerting its effect We concluded it is specific erythropoietic stimulus

DR ELIEL Perhaps we should treat polycythemia with castration and hypophysectomy

DR BAKER I don t think anybody has tried castration on these patients or treated them with estrogens

IV

RADIATION HYPOPHYSECTOMY

DR. A P M FORREST

IN the University Department of Surgery in the Western Infirmary Glasgow, we have recently developed a simple method of inserting radon seeds into the pituitary fossa by means of a cannula introduced under radiological control through the nose and sphenoidal sinus[21] We suggested that in this way it might be possible to avoid craniotomy and yet achieve complete and safe destruction of the pituitary, with benefit to patients with advanced cancer We have now treated forty five patients by this method including thirty six cases of breast cancer, and I feel honored to present our results at this symposium

All these patients have been in an advanced stage of malignant disease with multiple and widespread metastases in all cases disease had progressed despite surgery, radiation therapy and in most instances hormone measures They were subjected to pituitary implant only when the radiation therapists considered them unsuitable for further conventional treatment

In the first twenty six cases we followed our original technique the seeds being inserted through a single cannula introduced through the right nostril Histological examination of autopsy material revealed that our original dose of 10 mc in two seeds, even when centrally placed, was quite insufficient to destroy the gland and so in subsequent patients, the dose was increased to fifteen, and even, in some instances 20 mc As even 15 mc well placed may leave a rim of viable cells we have, in the last nine-

teen cases modified our technique to obtain a wider dis tribution of radiation within the gland The director ap paratus has been modified to accommodate two cannulas which are inserted simultaneously into the pituitary fossa one through either nostril Two seeds each of 8 mc , can thus be placed to lie symmetrically in the gland one to either side of the midline

Postoperative Course and Complications

Apart from transient headache in a few of our patients the immediate postoperative course has been uneventful and patients can be discharged from the hospital three to four days after the implant Antibiotic cover appears to have prevented the occurrence of infection The only complication but that a formidable one has been late radiation damage to the optic chiasma In five patients defects of the visual fields have developed in one to seven months after the implant Two patients ultimately became completely blind Visual damage would appear to develop more readily if seeds become positioned high up in the pituitary fossa This was liable to occur when several seeds were inserted through a single cannula the first being pushed onwards by that succeeding it Since adopt ing our improved technique in which only one seed is in serted through each cannula no further case of visual damage has occurred

Clinical Results

In nine patients with malignant disease other than can cer of the breast no benefit has resulted from pituitary implant In this group there were five patients with ma lignant melanoma three with advanced cancer of the uterus and one with sarcoma of the breast All continued to deteriorate and all are now dead

Of the thirty six patients with breast cancer treated by

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Of the thirty six patients with breast cancer treated by

pituitary implant, sixteen have died from advancing malignancy Three of these sixteen patients had striking relief of pain arising from skeletal metastases and one with paraplegia had returning sensation and voluntary movements in her limbs A further patient, who had a history of repeated cerebral thromboses died from a cerebral hemorrhage eleven weeks after the implant Eleven patients are alive without regression of their cancer, but six of them have been too recently treated for assessment Several have had subjective improvement

TABLE 19

Pituitary Radon Implant for Breast Cancer

Treated to 2/29/56	36 Patients
Cancer Not Improved	
ALIVE—Follow up under 2 months	6 patients
—*Follow up 2 to 9 months*	5 patients
DEAD FROM CANCER	16 patients
DEAD FROM OTHER CAUSE (Cerebral Hemorrhage at 3 months)	1 patient
Cancer Regressed	
ALIVE	7 patients
DEAD—(9 month)	1 patient

The remaining eight patients have derived considerable benefit from the implant with objective evidence of healing of their cancer In four, skeletal metastases have recalcified while the other patients have shown healing of recurrent skin nodules disappearance of pulmonary metastases, and cessation of convulsions caused by cerebral secondaries A large untreated primary tumor of the breast with skin ulceration and glandular metastases has regressed

Case 1 J S (48) This woman when admitted was bedridden and in great pain from spinal and other skeletal metastases Implant (10 mc) was performed in February 1955 Within two days marked relief of pain occurred and she was ambulant one week later Biochemical evidence of bone regeneration coincided with the

symptomatic relief She remained well for nine months when she developed new metastatic nodules in the mastectomy scar Bilateral adrenalectomy has now been carried out and the nodules have disappeared

Case 2 J M (49) This woman was admitted to the hospital in March 1955 with Jacksonian convulsions and deepening coma An untreated breast cancer of two years duration was present Pituitary implant (10 mc) was performed seven days after the onset of the convulsions The convulsions have not recurred and she remained in excellent health until February 1956 when she developed further advancement of her primary growth and skeletal metastases Bilateral adrenalectomy was carried out.

Case 3 H D (35) This woman who had multiple metastases in lymph nodes and bones was treated by implantation of 15 mc of radon in April 1955 The osseous metastases have recalcified and those in the lymph glands have regressed

Case 4 J C (53) Admitted with persistent cough and multiple pulmonary metastases this woman was submitted to radon implant (20 mc) in May 1955 The cough has ceased and x ray examination demonstrates that her metastases have completely regressed

Case 5 I McC (63) This woman with ulcerating nodules in her mastectomy scar and enlarged supraclavicular lymph glands was submitted to implant of 20 mc of radon in May 1955 The ulcers healed underlying skin nodules disappeared and the supraclavicular glands became smaller She remained well for nine months but contracted pneumonia from which she died

Case 6 M McN (50) This patient with skeletal metastases had pituitary implant (15 mc) in May 1955 She gained great relief from her severe pain and x ray examination reveals recalcification of the affected bones

Case 7 E S (66) This woman had an untreated massive growth of the breast with skin ulceration and enlarged axillary and supraclavicular glands Following implant

(15 mc) ın July 1955 rapıd healıng of the ulcerated area *and regressıon of tumor and glands have taken place*

Case 8 J D (48) Admıtted to hospıtal wıth great paın and ımmobılıty from skeletal metastases thıs patıent was treated by pıtuıtary ımplant (16 mc) ın October 1955 Symptomatıc relıef has occurred and the affected bones have commenced to recalcıfy

Hormone Effects

In those patıents who have undergone an adequate ım plant evıdence of hypopıtuıtarısm develops wıthın a few weeks Cortısone maıntenance therapy ıs requıred usual ly ın a dose of 25 mg per day and ıf thıs ıs wıthheld a *typıcal cortısone wıthdrawal syndrome develops wıth* anorexıa vomıtıng and great weakness Clınıcal sıgns of myxedema appear wıthın two or three months when tests of radıoactıve ıodıne uptake confırm the presence of hy pothyroıdısm A moderate rıse of serum cholesterol ıs noted after the fırst month and thıs ıncrease ıs maıntaıned Thyroıd replacement therapy ıs gıven The abılıty to promptly excrete a water load ıs lost

In most of our patıents dıabetes ınsıpıdus appears wıthın a few weeks of the ımplant and ıs frequently the earlıest sıgn of hypophyseal damage The severıty of the thırst and polyurıa ıs dependent upon the amount of cortı sone admınıstered and the urınary volume returns to nor mal levels when thıs drug ıs temporarıly wıthheld The dıabetes ınsıpıdus ıs seldom severe and can ıf necessary be controlled wıth pıtressın

When these patıents are on cortısone the output of 17 *ketosteroıds ın the urıne whıle lower than the* pre operatıve values ıs stıll consıderable When cortısone ıs wıthdrawn the output falls to levels of under 1 mg per day The urınary excretıon of pıtuıtary gonadotrophıns ceases followıng pıtuıtary ımplant Estrogens have dısap peared ın the urıne of the one patıent so tested

The effect of cortisone withdrawal on the clinical con dition and steroid excretion of these patients would ap pear to provide the most reliable indication of the extent of pituitary dysfunction

With one exception evidence of absent pituitary func tion has been obtained in all the eight patients who have shown regression of cancer The exception was one of the patients who relapsed ten months after implant The other patient who later was adrenalectomized also showed returned pituitary function at the time of relapse of her cancer The amount of radon implanted in these two pa tients was 10 mc since discovered to be insufficient to cause other than temporary depression of gland function

Many of the unsuccessfully treated patients did not survive long enough to allow adequate hormonal investi gations However, incomplete pituitary destruction was found in all of the ten patients who came to autopsy We therefore cannot say to what extent their lack of response depended upon 'hormone independence of their tumors It is first essential to devise a certain method of destroying the gland completely without risk of damage to the optic tract The use of the less penetrating radiation of an iso tope such as yttrium 90 might prove advantageous in this respect and is under trial

The dramatic improvement in eight of our patients has encouraged us to proceed with this method of treatment in the hope that with improvements in technique a larger number of patients may derive benefit

Addendum, July 1956

It is now established that a dose of radon sufficient to necrose the pituitary completely will damage more radio sensitive structures outside the pituitary fossa In one patient who died nine months after the implantation of 20 mc of radon areas of necrosis in the hypothalamus

were present The use of radon has been abandoned

Rods of irradiated yttrium oxide have now been introduced into the pituitary in eleven patients In nine of these, two rods each 6 by 2 mm and of 6 mc each have been inserted one into each half of the gland In one patient, an additional rod was inserted into the bottom of the fossa while in the eleventh, a patient with acromegaly and breast cancer four sources were placed within the grossly enlarged sella turcica In only two patients has post mortem examination of the pituitary been completed In one the patient with three sources the pituitary was necrosed except for a small area a few cells thick at the periphery In the other a patient with two 6 mc sources the gland was entirely destroyed

In two patients minor defects of the visual fields were discovered at routine ophthalmological survey one month after the implantation In both of these patients, the yttrium source was high in the fossa We now place the yttrium source 8 mm from the top of the sella turcica Only one patient in the yttrium series has had diabetes insipidus She had a small pituitary fossa and the rods were placed in the upper part In addition she had hyperphagia presumably caused by hypothalamic damage She died from progressive cancer two months after implantation Unfortunately permission for autopsy was not obtained

The high incidence of diabetes insipidus in the patients treated by radon implantation would suggest that radiation effects beyond the pituitary itself were a regular occurrence particularly in view of the absence of this complication following the implantation of yttrium It is interesting that the one patient in the yttrium group who had diabetes insipidus had other signs of damage to the hypothalamic structures

DR. DELBERT M. BERGENSTAL

During the past three years, surgical removal of the hypophysis has been carried out at this clinic on nine patients who had advanced metastatic cancer. The clinical response has been uniformly poor as far as the malignancy was concerned. There was no significant beneficial effect on the course of the tumors of these patients following hypophysectomy. At autopsy all of them had demonstrable significant amounts of residual pituitary tissue. In view of this experience it was believed that if hypophysectomy was to be useful for the control of certain types of metastatic carcinoma, some procedure had to be developed that could insure total hypophysectomy.

Development of Implant Procedure

These considerations led us to seek a different approach for destroying the hypophysis. The injection of radioactive colloid material, such as chromic phosphate or colloidal gold (Au^{198}), into the pituitary gland suggested itself as a possible alternative. This, however, was abandoned because we felt that there was too great a hazard of reflux of colloid along the needle tract and infundibular stalk producing damage to such adjacent structures as the optic nerves.

For this reason it was decided to use discrete radioactive sources such as those described by Kisielewski.[22] With these it was believed the location of the radiation fields could be better controlled. Yttrium 90 was chosen as the most suitable agent because of its strong beta radiation (2.3 mev), short half life (sixty two hours), and adequate activation cross section for thermal neutrons (1.24 barns). It was found that compressed pellets of yttrium oxide powder could be sintered at 1650° C. for an hour to produce solid ceramic pellets. These were formed as small

cylinders, 1 to 3 mm in length, to fit into a 17 gauge needle Activation of these pellets in a thermal neutron flux of 1×10^{13} n/cm²/sec for twenty four hours resulted in a specific activity of about 0 4 mc per milligram of yttrium oxide or 1 to 2 mc per pellet Some difficulty was experienced with long lived activity from rare earth contamination in the yttrium oxide Terbium 160 was the principal offender However, this contamination in the yttrium oxide that we used* was not of significant magnitude Handling the activated pellets presented no problem because a centimeter of water offers complete shielding against the beta radiation It was found that the pellets had a tendency to chip slightly when handled but this was prevented almost completely by coating them with a thin layer of lucite prior to activation

A 2 mm lead shield several centimeters long was placed around the proximal end of a 4 inch 17 gauge spinal puncture needle Under water the pellet was placed in the needle behind the lead shield This reduced the radiation level to less than 20 mrep per hour at the operator s finger tips and permitted the loaded needle to be handled without haste at the time of operation

Considerable effort was devoted to measurement of the radiation dosage in the tissue surrounding the pellet [3] This was accomplished with reasonable precision and isodose curves were constructed

Animal Experiments

A series of experiments was carried out in monkeys in which the hypophysis was reached through an anterior midline approach [23] Yttrium pellets of various sizes were inserted and after various intervals the animals were

* Obtained through the kindness of Dr Spedding University of Iowa

sacrificed and the resulting areas of destruction examined These were uniformly found to be spherical areas of complete necrosis 4 to 8 mm in diameter depending on the activity of the pellet surrounded by apparently normal tissue The zone of transition between normal and necrotic tissue was extremely narrow These findings are precisely what was anticipated from the isodose curves

TABLE 20

Radiation Dosage Required to Produce Necrosis

Anterior lobe of hypophysis	110 000 to 190 000 rep
Hypothalamus	60 000 to 120 000 rep
Optic chiasm or tract	60 000 to 140 000 rep
Oculomotor nerve	30 000 to 60 000 rep

The gradient of the radiation field is so steep that the transition from a cauterizing radiation dose to an insignificant dose must necessarily be sharp The apparent dose level at which transition occurred varied somewhat due probably to variations in the tissue swelling fixation artifact, etc The point at which necrosis occurred in the hypophysis and various parasellar structures is shown in Table 20

On the basis of measurements taken on typical human pituitary glands it was felt that the whole gland could be destroyed by four properly placed 1 mc pellets without risk of radiation damage to the neighboring structures

Preliminary Clinical Trials

After completion of the preliminary experiments on monkeys the clinical application of this procedure was first undertaken in February 1954 The patient was a 52 year old woman with carcinoma of the cervix that had metastasized and failed to respond to radiation therapy Four

0 88 mc yttrium beads were inserted into the sella On the following day, a 67 year old man who had had widespread disseminated cancer of the prostate that had responded previously but only temporarily to castration and estrogen therapy, was subjected to the same procedure Four 0 63 mc pellets were inserted into the sella

The first patient had a *smooth course* after operation until the fifth day at which time she began to show evidence of diabetes insipidus On the seventh postoperative day an increasing paresis of the left third and fourth cranial nerves was encountered and the lesion progressed to complete paralysis of these nerves Roentgenographs of the skull in the lateral and stereoaxial projection were obtained and revealed that all four beads were located in the posterior half of the sella turcica One bead had been placed well out to the left of the clinoid process These roentgenographic findings explained the diabetes insipidus as resulting from incomplete destruction of the hypophysis and the paresis of the left third and fourth cranial nerves from the misplaced pellet

The second patient failed to respond after operation remained comatose exhibited episodes of hypotension and hypothermia and expired on the fourteenth postoperative day

A second operation was performed on the first patient and two additional pellets of 0 75 mc activity were inserted into the sella Within four days after surgery the diabetes insipidus which had necessitated daily injections of 1 cc of pitressin began to decrease From that time until *the time of her death three months later,* no further evidence of diabetes insipidus was noted Roentgenographs on the tenth postoperative day after the second operation revealed that both of the additional pellets lay in the anterior sella

Roentgenographs that were taken on the second patient postmortem revealed that all four pellets were situated in the posterior half of the sella It became apparent that in the standard craniotomy position for exposure of the optic chiasm and sella turcica the angle of approach almost precluded placement of the beads in the anterior half of the sella if a straight needle was used The needles were then modified by curving the ends

Six patients were subsequently subjected to the procedure In each instance four pellets were placed within the bony sella Attempts were made to insert one pellet in the midline in the anterior portion of the sella two on either side of the midline in the midportion of the gland and one in the midline in the posterior aspect of the gland Of these four additional patients one died on the first postoperative day one survived four months and developed moderately severe diabetes insipidus on the eighth postoperative day which persisted until death and another survived eight months developing diabetes insipidus of moderate degree on the fourteenth day which decreased somewhat but was present to a slight degree until the time of death The last patient survived two months without evidence of diabetes insipidus No cranial nerve damage was noted in these patients

At this time it became apparent on the basis of autopsy findings that four pellets were not sufficient to yield anatomically complete hypophysectomy It also became obvious that the proper placement of the pellets in the pituitary was not as easily accomplished as had been thought Review of the histologic sections revealed that because of the sharp border of the region of radiation necrosis a pellet that deviated as little as 1 or 2 mm from its proper position left histologically undamaged pituitary remnants

It was then decided to increase the number of pellets Three additional patients were subjected to the procedure, and in each patient six pellets were inserted into the hy pophysis The intent at this time was to place four beads in the anterior half of the sella and two beads in the *posterior half Two of these patients died during the first* postoperative week The third survived five months and did not develop diabetes insipidus However, on the fourth postoperative day semi coma ensued which deepened for three days and then rapidly disappeared There was an associated transient paresis of the right sixth cranial nerve It seems probable that the altered consciousness and cra nial palsy were direct results of reversible radiation dam age

In the subsequent eight patients seven to eight radio active pellets averaging a total dose of 6 0 mc, were in serted into the sella Five of the seven operations were carried out using local anesthesia It was believed that because many of these patients had advanced metastatic lesions particularly to the lung and to the liver, the use of a general anesthetic would increase the hazard The un eventfulness of the course after operation may be due ma terially to the choice of the anesthetic We consider local anesthesia indicated in patients who are in poor preopera tive condition

One of the eight patients died suddenly one week after operation of a cause unrelated to the procedure One of the eight patients exhibited symptoms of cerebral edema for four days postoperatively After this period of time he improved rapidly and was asymptomatic by the eighth postoperative day No other complications were observed As pointed out previously the choice of anesthetic de pends upon the condition of the patient The procedure can be carried out quite easily under local anesthesia and

this should be the choice for patients who have wide spread hepatic or pulmonary metastases or in those patients whose preoperative condition is poor and in whom general anesthesia would increase the surgical risk For those patients who present a fairly stable general condition and in whom no specific contraindication exists the choice is endotracheal anesthesia

The surgical technique as used at present is essentially as follows A standard right frontal craniotomy is performed The infundibular stalk is always clipped and divided The stalk should be clipped as close to the hypothalamus as possible Eight to ten pellets of Y^{90} are inserted into the hypophysis four into the anterior most portion approximately 4 mm apart three in the midportion and three in the posterior region of the gland 4 mm apart

Results of Anatomical Studies

Twelve of the total of twenty patients have died and autopsies have been obtained on each of these The bony sella was removed in toto and the entire content of the sella was embedded Each of the preparations was sectioned serially Ten micron sections were obtained and every fortieth section was mounted and studied By this means an average of twenty to twenty five sections of each pituitary gland was studied to determine the completeness of the hypophysectomy The hypothalamus was likewise imbedded and studied

Observations of the specimens have revealed histologically normal appearing remnants of the pituitary gland in each of the twelve cases that came to autopsy The amount of this portion varied from patient to patient depending upon the number of pellets that had been inserted and their implantation site It became clear that in the major

ity of instances these remnants of functioning pituitary tissue are present usually in the lateral extremities of the gland close to the dural covering and usually in either the anterior or posterior most portion on the right side These areas escaped radiation destruction because one or the other beads was placed as little as 1 mm from its proper locus The demarcation between completely necrosed pituitary tissue and normal appearing tissue is extremely sharp so that precise positioning of the pellets is of paramount importance to obtain complete destruction of all pituitary tissue

Clinical Results

A brief discussion has been given of certain patients in the preceding discussion mainly to point out the application of the technique of placing the Y^{90} pellets and postoperative complications that have been observed

It seems clear that further research is necessary to develop better methods of placement of the Y^{90} pellets if adequate hypophysectomy is to be achieved Increasing the number of pellets (ten to twelve are now used) has helped to accomplish greater destruction since the overlapping and extension of the radiation fields tend to destroy more pituitary tissue

In the last 14 months we have done nineteen Y^{90} hypophysectomies for metastatic carcinoma of the breast Many of these had only four to six pellets placed in the pituitary gland and no remissions in this group were seen At autopsy sectioning of the pituitary showed small areas of cells which were not necrotic In the group of patients still living there are five who have had excellent objective regression of their lesions One of these patients had relapsed after adrenalectomy and showed remission following the hypophysectomy Three of these patients

have had remissions of over a year others showing regression have been followed for only three to five months

There does not appear to be any single group of endocrine tests that will yield unequivocal proof of the completeness of hypophysectomy We have observed the development of pituitary myxedema in six patients who had had hypophysectomy and at autopsy were found to have small amounts of anterior pituitary tissue remaining in the pituitary fossa The patients who have had intact adrenals at the time of hypophysectomy have on occasion been maintained without any adrenal hormone replacement for brief periods During this period they did not have a sense of well being nor a good appetite However their electrolyte balance remained essentially normal and their blood pressure although somewhat lowered did not reach shock levels In at least six patients who were maintained on a very small maintenance dose of DOCA and/or cortisone there were rather stressful reactions secondary to complications from the metastatic carcinoma During these periods they developed symptoms of what appeared to be adrenal insufficiency with low serum sodiums and hypotension

The onset of diabetes insipidus occurs shortly after operation and it does seem clear that all of the patients who had significant amounts of anterior pituitary tissue remaining in the pituitary fossa following hypophysectomy developed moderate diabetes insipidus There have been a few patients in whom the diabetes insipidus gradually disappeared However these patients still did not have normal water or solute balance

The preoperative and postoperative hormonal support for the patient undergoing hypophysectomy is accomplished quite easily The day before surgery the patient is given intramuscularly 100 mg of cortisone acetate On

ity of instances these remnants of functioning pituitary tissue are present usually in the lateral extremities of the gland, close to the dural covering and usually in either the anterior or posterior most portion on the right side These areas escaped radiation destruction because one or the other beads was placed as little as 1 mm from its proper locus The demarcation between completely ne crosed pituitary tissue and normal appearing tissue is ex tremely sharp so that precise positioning of the pellets is of paramount importance to obtain complete destruction of all pituitary tissue

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DR JOSEPH P EVANS

I should first like to say how delighted I am to have been included in this conference which has been so stimulating and productive I am a latecomer in this field Dr Bergenstal has reported to you on the work carried out at the University of Chicago by him and by Dr Theodore Rasmussen before the latter s departure for the Montreal Neurological Institute and he has told you of the role played by Dr Paul Harper in the development of the yttrium technique Subsequent to the departure of Dr Rasmussen in May 1954 a number of additional yttrium hypophysectomies were done by Dr Eric Yuhl and he continued to do most of them following my transfer to the University in October 1954 until his departure in June 1955 when I assumed full responsibility for the operative procedure

Operative Procedure

I shall address myself entirely to the matter of the surgical problems because Dr Bergenstal has already covered the other aspects As already noted Dr Rasmussen had not been happy with the results of his own efforts at removal of the hypophysis by the standard surgical techniques Dr Harper and he thought that it might be possible using a beta emitter such as yttrium to secure complete destruction of the gland with less bleeding less danger to the optic nerves and less prolonged retraction of the frontal lobe than is inherent in the method of surgical hypophysectomy Though experienced of course in the removal of tumors of the pituitary gland I have not had occasion to carry out surgical hypophysectomy and I am full of admiration for the results which Dr Ray has reported and also for those in the smaller group that Dr Matson has done Our own results are not so good but I

the day of operation, the patient is given intramuscular injections of 150 mg of cortisone acetate before the opera tion Following operation cortisone acetate is continued at 50 mg every six hours for twenty four hours beginning the first day On the subsequent days the doses of corti sone acetate are reduced to about 150 mg on the second day 100 mg on the third 75 mg on the fourth and then 50 mg a day as maintenance therapy Lower maintenance doses of 25 to 37 5 mg have been used successfully In tramuscular injections of pitressin (0 5 to 1 0 ml) or nasal insufflation of pitressin is used to control diabetes insipidus when it is symptomatic

tomies and thirty-one yttrium hypophysectomies of which nineteen have been done for carcinoma of the female breast Five of these latter patients are living Of the cases for which I personally have been responsible there have been three early deaths One of these does not belong in the series under discussion having been an instance of male carcinoma of the breast which I unwisely chose to do The patient died the following day and was found to have a large metastasis in the medulla He should not have been subjected to operation In the nineteen cases of female breast carcinoma under discussion there have been two operative deaths I have already referred to the difficulty that I experienced initially in placing the beads satisfactorily In the effort to correct this situation I elected to turn a bifrontal flap The underlying dura was very adherent to the bone and two of the frontal veins described yesterday by Dr Ray were torn and required clipping This led to swelling of the frontal lobe and frontal lobe amputation became necessary Trouble was experienced with the anterior cerebral artery and the patient died on the operating table In another instance that of an elderly woman with advanced cerebroarteriosclerosis which was the first case in which the revolver device was used delay was experienced in the loading of the gun and retraction of the frontal lobe was maintained unduly long The patient died some five days later of softening of the frontal lobe

These then are mistakes which we have slowly learned to recognize and I believe now can satisfactorily avoid

It should be reported that we have produced some extra-ocular palsies by this technique four in all Two of the nerve palsies produced have been noted immediately postoperatively and it seems evident that we must have slipped our needle out of the confines of the sella and mechanically interrupted the third or the sixth nerve In one

believe this fact may be attributed at least in part to the fact that three surgeons in turn have been learning this rather exacting technique

The exposure of the gland has been exactly that described yesterday and shown so beautifully in the movie except that we have not used Arfonad and we have employed a lumbar catheter for drainage of the cerebrospinal fluid

The yttrium implants have been teased into the sharp end of the large lumbar puncture needle and with a nylon stilet were pushed up under the lead shield Loading is done under water and the lead shield protects the surgeon s hands from irradiation When using this method we employed six ten or twelve needles and though these were placed near at hand it was necessary for the surgeon to take his eyes from the field on each shift of needles Since we were having difficulty in dispersing the yttrium beads throughout the gland Dr Harper developed a gun made up of a lucite barrel with a rotating disc permitting the loading of twelve pellets This device made it possible to place the beads without taking one s eyes from the field It has seemed to us that this has helped in the more accurate placement of the beads though we are still having trouble in securing accurate placement

In general I believe we may say that there has been only one case in which judging by the x ray evidence of placement of the beads we could anticipate complete destruction of the gland Serial sections in this particular case are not yet available I believe however that it will be possible to master the technical aspects of this problem and to achieve satisfactory distribution of the implants

Mortality and Morbidity

As Dr Bergenstal has indicated there have been done at the University of Chicago nine surgical hypophysec

DR JAMES J NICKSON

First I would like to say that Dr Woolley has very kindly consented to discuss the effects of irradiation upon the cells of the pituitary gland using differential staining techniques

If one assumes that alteration of pituitary function is useful in the management of carcinoma of the breast then the question arises as to the role of pituitary radiation as a means to that end One can consider in abstract what would be desirable from this point of view Clearly suppression of the functions of the gland without modification of the function of structures around the pituitary is the optimal position This turns out to be a rigorous qualification We know very little indeed about the time dose interrelationships of radiation and modification of the functions of the pituitary

The pituitary may be irradiated by one of two general methods Implantation of sources of radioactivity into the gland is one of these and it was discussed this morning The question of dose distribution within the pituitary is a crucial one If only one or two pellets are used the probability that some of the pituitary cells will survive due to inadequate irradiation is high in the light of the studies reported here Even with the order of ten pellets being used some pituitary function may well remain Undoubtedly some of the difficulty is technical that of reducing theory to practice inherent in the development of any new technique I would like in passing to raise the possibility that with a relatively limited number of sources a continuing dosimetry problem will continue to exist and to suggest that the use of a larger number of pellets —an infinite number—might give a more uniform dose to all of the pituitary and hence a greater chance of killing all of its cells This would be the application of the

ınstance, a patıent upon whom I operated under local anesthesıa, the sıxth nerve paresıs was evıdent as soon as the drapes were removed

In the effort to avoıd thıs complıcatıon small metal beads have been placed near the end of our needles so that we cannot push the needle too deeply In one ın stance a mısplaced bead produced some numbness ın the dıstrıbutıon of the first dıvısıon of the trıgemınal nerve In two patıents there has been some reductıon ın vısual acuıty I should attrıbute thıs to handlıng of the optıc nerve rather than radıatıon, ın both ınstances A post operatıve clot requıred re elevatıon of the flap ın one ın stance and ın thıs partıcular case there was a good deal of mental bluntıng the patıent s behavıor after the second procedure was very much akın to that seen ın some pa tıents after prefrontal lobotomy

Our technıcal procedure ıs now carrıed out more smoothly An x ray film tunnel ıs placed under the pa tıent s head at the start of the procedure and after four to sıx beads have been placed theır posıtıon ıs checked A lateral vıew ıs obtaıned at the same tıme In some ın stances we have made a second check two thırds of the way through the placement of beads The objectıonable feature of the x ray check ıs that ıt requıres tıme and lengthens the perıod of retractıon of the lobe

We dıscuss the employment of a stereotaxıc devıce but ıt has been my belıef that thıs would not add enough to warrant the dıfficultıes entaıled I feel quıte confident that one can learn to place the beads accurately

post radiation At the other end of the time scale, we know from Lampe s [4] work in medulloblastoma as late as ten or more years after irradiation lasting and crippling changes in the central nervous system can make them selves evident

Operative Procedure

Our observations here related to the use of a 22 mil lion volt x ray beam for irradiation of the pituitary and hypothalamus We irradiated both structures primarily because of the observation of Arnold[25] of the University of Illinois from his monkeys using in his instance the elec tron beam The patients were treated for the most part during the second half of 1954 We have treated no pa tients since December of that year

Our interest in this study arose out of two things 1) We were able to work with Dr Pearson s excellent group and so could look at end organ function in an orderly systematic way that would give us a reasonably sensitive index of pituitary hypothalamic change in the post radia tion state thus permitting us to state with some definite ness whether radiation as given did or did not modify function of these structures Without getting into too much discussion from the radiological point of view I do not believe there is any biological difference between the electron beam and photon beam here 2) Arnold observed in his monkeys irradiated with betatron produced electron beams changes which he interpreted as indicating long range depression of function as measured by clinical ob servation of end organ effects Histological changes were unquestionably present in the hypopathalamus in irradi ated monkeys We then felt that initially we should ir radiate both the hypothalamus and pituitary feeling that if no change occurred there was little point in pursuing

packing technique used for the treatment of cancer corpus uteri to the pituitary fossa If the normal tissues around the pituitary are to be preserved we will have to confine our efforts ultimately to beta ray sources in order to reduce the dose to the normal tissues as much as possible I think the use of gamma sources will in retrospect be no more than a phase in the development of the technique

External Beam Irradiation

External beams of radiation may also be used A beam of positively charged particles may be used The Berkeley group is the only one with experience with this class of external beam irradiation They have used protons A beam of x rays may also be used We here have had some experience with this form of pituitary irradiation Before considering the results I would like to consider briefly some of the theoretical problems of any external beam treatment The problem of damage to the intervening or adjacent normal tissues is paramount predominantly the optic nerve tract chiasm and frontal lobe or other portion of the normal brain structure that is being exposed to the beam The whole question of central nervous system responsivity to radiation is up in the air again For many years it has been regarded as essentially unresponsive to the effects of radiation We now know that this is incorrect Various portions of the central nervous system are sensitive and marked and serious alterations can occur both as a result of vascular and parenchymal primary processes

The whole question of time dose relationships and the appearance of radiation damage is not yet understood Early changes have been noted In a month definite changes in at least one of our patients could be seen

mus axis We therefore started with relatively low doses 6 000 r in about twelve to fourteen days We saw no acute adverse effects We therefore increased the dose in step wise fashion the last two cases receiving 15 000 r in a period of three weeks We felt the classical pharmacologic procedure of pushing on until toxicity developed was about the only way to arrive at the maximum acutely tol erated dose

Casts were made for these patients and were used with a back pointing technique for setting up the patient The actual treatment field size was 5 by 5 cm which included hypothalamus and the pituitary as indicated by the sella

Clinical Results

Six patients did not show evidence of end organ re sponse Many of them lived an insufficient period of time to permit response to appear we did not see any evidence of positive modification of end organ response in less than six weeks with the external radiation This time lag fits in a general way with many other kinds of response to irradiation Of the six who responded all showed changes in the urinary FSH Only two showed changes in 17 ke tosteroid levels One showed a queer change in iodine uptake As to protein bound iodine two showed a definite effect and one a questionable effect One showed a modi fication of glucose tolerance none of the others did One was not tested Four of the six patients showed a definite suppression or diminution in menses One showed a ques tionable effect and one had been surgically castrated prior to irradiation and hence was not available for evaluation

In only one patient did we have evidence of tumor response One showed a transient regression of skin nod ules This patient died in the hospital

As to acute side effects some patients had nausea and

one or the other If changes were noted, then we had the job of sorting out whether irradiation of the pituitary or of the hypothalamus was primarily responsible for the change

We used the 22 mev beam because we wanted to do a relatively simple en bloc irradiation of both pituitary and hypothalamus It gave the depth dose distribution A 22 mev beam is also rather better and easier to control in the radiation of the area in question

We had twelve patients in all nine with breast cancer two with carcinoma of the testis, and one with melanoma These patients were all suitable for surgical hypophysectomy We did not of course use cases of early disease The patients were followed for end organ effect by Dr Pearson s group

TABLE 21

Time Dose Relationships

TREATMENT TIME	
Maximum—28 days	
Minimum—12 days	
Average—17 2 days	
Dose	*No Cases*
15 000 r	2
12 500 r	2
10 000 r	2
8 000 r	2
7 000 r	1
6 500 r	1
6 000 r	2
	12
AVERAGE DOSE = 9 700 r	
MAXIMUM DOSE = 15 000 r	
MINIMUM DOSE = 6 000 r	

The optimal time dose interrelationships were unknown for external beams either in terms of normal central nervous system tissues or of the normal pituitary hypothala

patients should have shown changes had they lived long enough for them to develop

I will return then to the initial comment The question of modification of the pituitary by radiation other than in cauterizing doses is still really unanswered particularly in terms of time and dose With major amounts of energy from external x ray beams we have I believe only suggestive evidence of modification of pituitary function

I would now like to ask Dr Woolley if he would discuss the histologic changes that he saw in the pituitary specimens available to him

two showed nausea with vomitng The majority had headaches, the real reason for which I do not know Sub acute effects were weakness, fatigue and some epilation although none of these patents went on to a moist re action *in spite of the very high dose* I think this is a

TABLE 22

	Primary Diagnosis	*Dose*	*Time in Days*	*Urinary FSH*	*17 Keto Steroids*	*I Uptake*	*PBI*	*Glucose Tolerance*	*Insulin Tolerance*	*H O Tolerance*	*Menses*
L B *	Ca of Breast	15 000 r	21	+	+	0	+	NR	NR	NR	Surgical Castration
R F	Ca of Breast	8 000 r	15	+	+	0	0	0	0	0	+
J McG	Ca of Breast	10 000 r	12	+	0	0	0	0	0	0	+
B S	Ca of Breast	10 000 r	15	+	0	0	+	0	0	0	±
E S	Ca of Breast	6 400 r	14	+	0	±	±	+	NR	0	+
S S	Ca of Breast	12,500 r	20	+	0	0	0	NR	NR	0	+

* Betatron therapy after partial hypophysectomy
\+ = Response
0 = No response
NR = Test not repeated

function of the size of the field being used There is an other parameter that is important modest pigmentation of the skin was found

Two patients developed abnormal electroencephalo grams Two developed blindness one complete and one partial Three showed mental deterioration I think all

DISCUSSION

Dr Lipsett Dr Forrest what is the dose distribution around the radon seeds?

Dr Forrest Our initial dose of 10 mc was based on that used by Pattison and Swan [6] for direct implantation of the pituitary at craniotomy As a result of this insufficient extent of necrosis found at autopsy this dose was increased with the production of damage to structures outside the sella turcica

Dr Eliel In the patient who developed skin nodules after pituitary implant what was the evidence of recovery of pituitary function?

Dr Forrest When this patient (Case 1 J S) developed her skin nodules we stopped her cortisone and she remained well excreting on the average 3 mg of ketosteroids a day She had only 10 mc radon implant, which we now know to be an inadequate dose

Dr Kennedy In your second patient the one with brain metastases could this conceivably be an effect such as Dr Taylor describes in the patients with brain metastases that he treats with prednisone Is it possible that you are simply getting local regression in the brain lesion as a result of the cortisone administration?

Dr Forrest I agree that we have no objective evidence of regression of this patient s cerebral secondaries—her convulsions may have been due to hemorrhage in the brain metastasis At the time of her relapse she also could be maintained without cortisone and during that time she excreted 5 to 8 mg of 17 ketosteroids per twenty four hours and 8 mg of total estrogens Her iodine uptake during that time was normal

Chairman Pearson Was cortisone given initially in this case?

Dr Forrest Cortisone was started twelve days after the implant

Dr Baker When these patients are examined at autopsy Dr Forrest what do the residual pituitary cells look like?

Dr Forrest Dr A T Sandison who is interested in the pathology of our cases is of the opinion that the remaining pituitary cells are histologically indistinguishable from normal pituitary One striking feature is the absence of any reaction around the zone of necrosis—only necrotic tissue surrounded by normal looking pituitary cells with a sharp line of demarcation

I received four pituitaries from individuals that had had radiation directly to the pituitary and attempted to differentiate different cells in these pituitaries The common technique of course is to differentiate at least three cell types the so called chromophobe, acidophil, and basophil We went one step further and divided the basophils into the beta and the delta cells sometimes called gonadotrophic and thyrotrophic or descriptively, a round coarsely granular basophil and finely granular angular shaped basophil We did see differences between these pituitaries and what we thought should be the normal condition The changes in the irradiated pituitaries appeared to reflect damage to the secretory cells

consequent radiation near to the optic tracts The insertion of two seeds each through separate cannulas introduced on either side prevents this possibility and allows more accurate positioning of the source Furthermore as a wider distribution of dose within the gland is obtained the total dose can be reduced Finally the use of the less penetrating radiation of yttrium^{90} to produce necrosis should greatly reduce the risk of visual disturbance

DR MATSON So it is going to be unpredictable?

DR FORREST It is a risk that is always going to be present.

DR WEST Dr Charles Harrold of our Head and Neck Service has removed the pituitary by a transphenoidal approach He had quite a bit of difficulty with hemorrhage It seemed that this was due to connecting sinuses on the anterior wall of the sella I gather from what you said hemorrhage has not been a problem?

DR FORREST We do not pack the nose and have had no trouble with hemorrhage The trauma caused by the insertion of a 2 mm cannula is very slight compared to that of a transphenoidal hypophysectomy

DR MATSON *Dr Evans in your procedure do you inject* through or tear the diaphragm?

DR EVANS The needle is inserted through the diaphragm

DR MATSON The diaphragm varies so from case to case

DR EVANS In one instance a bridged sella gave us considerable difficulty because the area through which the needles could be inserted was reduced in size As a result of that experience I think I could achieve a satisfactory distribution of beads in another comparable case

DR MATSON How big is the needle?

DR EVANS A 17 gauge

DR RAY The curve on the end makes it possible to place the bead directly?

DR EVANS We use straight needles to place the beads posteriorly and a curved needle to place it in the central area and behind the tuberculum sella

DR RAY You make more than one puncture?

DR EVANS Yes we expose the diaphragm and clip the pituitary stalk which we have not been dividing Once the diaphragm is exposed it is not too difficult to see where the needle should be inserted We usually place the posterior ones first often one centrally and then one on each side Switching to the curved needle

Dr Jessiman We all realize that this technique needs the skill not only of a surgeon but also of a good radiation therapist Sir Stanford Cade with whom I was associated was very impressed by Dr Forrest s work and saw this technique being used in Glas gow He had the necessary equipment made and is using this technique in London

I would not like to report his figures with authority here but my impression is that he has done twenty-one cases Of these about four developed visual disturbances including blindness A further group I believe four developed rhinorrhea and menin gitis There was one dramatic remission

The complications reported by others using this technique point up the skill and care with which Dr Forrest has placed his radon seeds

Such attention to detail is essential if the results are to be good and the complications few in the same way that surgical hy pophysectomy needs good surgical care if the results are to be good

Dr Forrest The accurate positioning of seeds depends on good radiological control In London gold grains are being im planted into the pituitary with the aid of the image intensifier which permits great accuracy and eliminates the time taken to develop several radiographs

Dr Forrest The insertion of small multiple sources as sug gested by Dr Nickson by our technique would entail multiple punctures of the sella turcica by a small bore instrument It could be done

Dr Evans It seems to me the difficulty of your method is that you don t have much latitude

Dr Forrest If small bore stout cannulas were used the sella could be punctured in several places through each nostril The depth of penetration can easily be varied

Dr Kennedy Dr Forrest have any of your patients had rhinorrhea?

Dr Forrest We have had only one case in which the can nula tapped cerebrospinal fluid at the time of implantation

Dr Ray What is the difference now in the technique that prevents visual impairment? I am not clear about that

Dr Forrest In the original technique several seeds were in serted through a single cannula This allowed the possibility of a seed being pushed high up in the fossa by that following it with

DR FORREST We recently obtained some yttrium metal but we have not yet attempted to form it into rods It is more expensive than the oxide

DR NICKSON Have you speculated about the use of solution?

DR FORREST We attempted to inject a radio-opaque oil through the nasal cannula but it failed to diffuse through the pituitary and finally leaked back along the cannula It would be dangerous to attempt to instill radioactive material in this way

DR RAY Dr Bergenstal did you actually try chromic phosphate?

DR BERGENSTAL Our only experience has been at autopsy Dr Yuhl tried to inject non radioactive chromic phosphate mixed in dye and found that he had no success at all It refluxed every time he attempted to inject it and as a result, we did not actually try it

DR LUFT We injected 10 mc chromic phosphate with methylene blue to insure that it did not come out in the arachnoid space One of the patients died shortly afterwards We knew she was going to die She had a big mass in the mediastinum We got activity all over the body It was absorbed The highest activity was in the sella in the pituitary We looked at the pituitary two days later We could not see very much The second patient was operated on the same day She is still alive four months after the operation The soft tissue metastases are gone but she has more skeletal metastases than before When we found that activity could be detected all over the body we went in and tried to remove the hypophysis The tissue in the sella was found to be extremely brittle It could not be removed A biopsy was taken Microscopic examination disclosed advanced necrosis of all cells

DR EVANS We thought a good deal about this matter Dr Yuhl injected chromic phosphate into tissues in the laboratory and found there was always reflux

DR LUFT We injected different spots about 1 cc or 2 cc got in

DR EVANS Knowing how difficult it is to place beads I would think it also might be very difficult to inject the chromic phosphate accurately With each puncture one increases the chance of reflux

DR ELIEL We have raised the question of chromic phosphate injection of the pituitary Tables 23 and 24 present the results in

we then try to place another row of three in the central portion of the gland and then still using the curved needle attempt to place three behind the tuberculum The remaining beads may be placed according to need following the x ray check

DR MATSON Have you done serial x rays for a week or ten days?

DR EVANS Postoperative films are usually made a week to ten days following the procedure In my experience the beads do not move within the sella but when inserted beyond the limits of the sella I am sure they do move

DR LIPSETT In the area of necrosis do you have the ordinary phagocytic response?

DR EVANS The cauterizing destroys pretty much all the elements

DR RAY Dr Forrest in the cases autopsied have you seen any suggestion that there has been some reaction in the wall of the cavernous sinus?

DR FORREST None that has been looked for specifically

DR RAY One of the thoughts that many have had is if you get the dosage high enough and you get a bead up against the cavernous sinus there is a possibility of a necrosis and rupture of the sinus

DR BERGENSTAL We have had none of that

DR RAY Perhaps it is not too serious and the sinus may seal off

DR BERGENSTAL I think it will be most interesting to see the effects of what we believe is a tremendous dose of yttrium In our first patients we have not gone beyond 5 or 6 mc This is predicated on the work in monkeys It may be that much better results can be obtained with higher activity We have been so afraid of hypothalamic damage we have not done it

DR MATSON Did not Dr Rasmussen report a couple of your patients went to sleep after three or four days?

DR BERGENSTAL One patient did We do not have proof that that was owing to hypothalamic damage

DR EVANS We have not had real trouble

DR NICKSON Returning briefly to your dosage estimation I did not hear what you said you used as a standard for yttrium

DR BERGENSTAL Uranium oxide 238

DR FORREST Have you had any experience with yttrium metal?

DR BERGENSTAL No

cases there has been some reduction in ketosteroids although the measurements in the second case are probably not significant. Diabetes insipidus is thought to be present in Case 2 although that has not been tested with measurement of solute load or with the Carter Robbins test.

As Dr Luft indicated, radioactive phosphorus has been found both in blood and spinal fluid in both cases I dont have the data

TABLE 24

Intrahypophyseal Instillation of Cr P^{32} 0 in Ca of Prostate
Physiologic Data

Case	I^{131} % uptake			17 KS mg /24 hr		Diab Insip	P^{32} Blood SF
	0	3	6 wks	Pre	Post		
1	5		10	4.5	0 0	0	+
2	27	0 4	12	2.5	0.2	±	+
3						0	

on the third case because that operation was performed so recently It was not possible to estimate accurately the amount which was circulating in those fluids since the distribution of phosphorus is so difficult to measure However they felt it was probably less than 10 per cent of the total administered dose

Doctor Are you going on with it?

Dr Eliel I dont think they have been thoroughly discouraged They are going to try a higher dose of radioactive phosphorus and try to concentrate it into a much smaller concentration

Dr Lipsett When Dr Jaffe-[7] first started doing this his group decided to use a little larger dosage They thought they could distend the sella to take the chromic phosphate They observed nerve palsy and some loss of visual acuity rather soon after the injection of chromic phosphate I dont know whether they continued it or not. But they did use methylene blue in a few of these cases using between 1 5 and 2 cc and did not get reflux during the time that the diaphragm of the sella was exposed

Dr Baker In your monkeys I wonder if you ever considered using an alkylating agent, to see if it would go through the sella. Most of it is fixed to tissue in ten minutes

a group of three cases done at the Veterans Hospital Oklahoma City I have not been associated with the project but am presenting their results All three patients had advanced carcinoma of the prostate The doses administered were 7 mc in Case 1 and 11 mc in Case 2 The volume of 3 cc was used in Case 1 which is obviously unsuitable just from volume consideration and there must have been reflux The second case it was concentrated to a

TABLE 23

Intrahypophyseal Instillation of Cr P[32] 0 in Ca of Prostate Clinical Results

Case	*Pain Relief*	*Headache Post op*	*Tumor Regr Ac P'Ase*	*Comment*
1	+	+	?	Hemiplegia
2	+	+	+	Castrated pre-op
3	+	+	?	Transient hemiplegia

volume of 1 5 cc That also seems to reflux further concentration apparently should be used

The patients have all experienced relief of pain The first two were bedridden and were able to get out of bed because of pain relief However you will note the second patient was castrated one month preoperatively so we cannot say there was any improvement due to the installation of the chromic phosphate He has had postoperative headache which it was felt was more than one could expect from craniotomy alone The only evidence of tumor regression is in the patient who was castrated Hemiplegia in one case came on about a month postoperatively and it is not known whether or not it can be related to the chromic phosphate injection A transient hemiplegia also followed very shortly after the isotope injection in Case 3

There are rather inadequate physiologic data on these patients I^{131} uptake was measured preoperatively and three and six weeks postoperatively In Case 1 you see there is normal I^{131} uptake at six weeks The second patient had a reduction in I^{131} uptake virtually to zero in three weeks and recovery at six weeks In both

phosphate in a plastic envelope and put it in the sella and fix it there with muscle or oxidized cellulose so that the rim which may be left behind in the best surgical operation could be inactivated

DR BERGENSTAL Dr Harper has been working on such a little balloon that would fit in the sella with a small plastic tube coming out in which he hoped to instill radioactive iodine if nothing else and later take it out

DR MATSON You would have to stuff it in with something which could be moulded

DR MATSON The sella is not round

DR NICKSON Use fluid

DR BERGENSTAL There are crevasses and you have to push it out

DR EVANS In order to use such a device one must employ lead in tubes which must pass the optic nerve in gaining access I favor leaving the matrix of the gland intact so that there is sub stance in which to set the beads Conceivably some type of sponge might be developed which could be loaded with yttrium following surgical hypophysectomy The sponge could then be inserted into the evacuated sella There might still however be considerable difficulty in obtaining a satisfactory distribution of the beads with in the sella

DR LIPSETT Dr Ray has a sponge with fluid running into it

DR KENNEDY Could you lay beads along the edge and pack with muscle?

DR MATSON You would have to fix them better than that I wonder if you had a solid mass something like oxidized cellulose with beads sewed on the surface if you could really have some thing quite firm to work with

DR ELIEL One of our group made an interesting suggestion just before I came and that was to use radioactive Zenker s solu tion radioactive mercury That has a rather low energy gamma radiation of about 2 mev I think a half life of two and one half days We did not actually make any calculations as to the dosim etry It might be difficult to fix enough mercury to get adequate radiation dose Let it sit in there half an hour during the operation and you might achieve it

DR MATSON I don t think liquid media appeal to the neuro surgeons very much We value the tips of the fingers The hazard would be quite great

DR ELIEL We have thought of putting solid chromic phos

DR NICKSON I *would like to discuss* Dr Baker s *comment on* an alkylating agent In essence one has to ablate the pituitary whether by surgery or radiation or cauterization Cautery is one form of noxious agent radiation is only another form of noxious agent that can be used I think perhaps broadening our horizons a bit we may find an agent that will destroy pituitary tissue but still be compatible to normal structures around it

DR FORREST We have constructed two electrodes that can be passed into the pituitary along the cannulas across which one could pass a high frequency current By this method a good area of necrosis can be produced in the rat liver but we have not yet had the opportunity to test it in the human

DR LUFT We tried electrocoagulation five years ago in a patient with Cushings disease I had followed that patient for ten years she was in an advanced state of disease Dr Olivecrona electrocoagulated the pituitary Four weeks later she had her first menstruation in six years A few months later she was pregnant I saw her recently and she is doing fine She is quite normal now with normal blood pressure no osteoporosis no diabetes and she is menstruating normally

DR MATSON Did he cut the stalk?

DR LUFT I don t know We have been debating whether or not the stalk was clipped I do not think it was

DR KENNEDY Dr Evans how much local trauma to the pituitary do you get just from inserting the needles and beads?

DR EVANS I would think, virtually none but I don t know

DR KENNEDY In one of our patients Dr Peyton inserted a needle three times into the fossa to aspirate the pituitary There was gross bleeding

DR BERGENSTAL We don t see excessive bleeding after we put the needles in

DR EVANS Not unless we put the needle through the wall of *the sinus In that instance there may be back bleeding* but it is very easy to control and we have found that a little gel foam placed over the point of needle insertion will stop the bleeding

DR MATSON What you need is a combination of two methods Certainly my feeling is that it is not much harder to take out two thirds of the pituitary than it is to expose it I don t think there is any additional hazard really now to tearing the diaphragm and taking the bulk of the pituitary gland out Possibly then one could somehow fix the yttrium beads or get a thin layer of chromic

phosphate in a plastic envelope and put it in the sella and fix it there with muscle or oxidized cellulose so that the rim which may be left behind in the best surgical operation could be inactivated

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Dr Matson I don t think liquid media appeal to the neurosurgeons very much We value the tips of the fingers The hazard would be quite great

Dr Eliel We have thought of putting solid chromic phos

phate in some kind of pliable film a balloon type thing There again you get into dosage problems from the folding of the plastic membranes in a spherical cavity Actually when you fold the film you triple the layer of solid isotope

DR MATSON I think you need something bigger than the sella to stuff in

DR RAY The sella is not globular There are recesses particularly in front of the optic nerve and if you use a balloon it pouches out in all directions and is probably going to pouch out through the opening There are technical difficulties and it is not as simple as it appears

DR ELIEL What about imbedding chromic phosphate in bone wax and stuffing that in?

DR RAY One might stuff moldable material in the sella and devise means to have it stay in there perhaps put a couple of sutures across the top to keep it from slipping out

DR ELIEL If a sphere of bone wax that size were put in is there any danger from a foreign body reaction? Might necrosis follow?

DR RAY I don t think it would be well tolerated

DR FORREST We had considered removing some pituitary tissue through our cannulas and then injecting a quick setting plastic or alginate containing an isotope into the space We are first waiting to see what yttrium does

DR BERGENSTAL Our study started because we were not able to get complete hypophysectomy surgically Maybe Dr Ray has essentially solved our problem by an excellent surgical procedure Maybe it is now possible to do a really complete hypophysectomy surgically I don t think we will know until Dr Pearson has a better chance of re evaluating the patients when they relapse to determine if there is any evidence of a return of pituitary function That may be all we need

DR RAY Someone suggested to me that he had been hypophysectomizing animals by using steel wool as an abrasive We are getting tantalum fine mesh wool that I thought I might use for such purpose at the end of the operation Also the mesh could be touched with endothermy to cause coagulation of the lining of the sella

DR MATSON Carbon dioxide snow has been mentioned

DR LUFT We have been trying sodium hydroxide now for

some time in order to get rid of the last remnants of pituitary tissue We clear out the sella first with sodium hydroxide and then with Zenker s solution

CHAIRMAN PEARSON Along this line we have to consider the nasal pharyngeal pituitary too We have one patient a postmeno pausal woman who following hypophysectomy had a remission lasting about nine months She then relapsed We then took out first her ovaries and then two weeks later her adrenals She ob tained no improvement from this

DR LIPSETT We do not have enough data to answer Dr Bergenstal s question as to whether or not the completely hy pophysectomized patients will relapse Patients who have had complete hypophysectomies by serial section of the sella turcica have subsequently relapsed Unless the nasal pituitary is function ing we have to conclude that the patients who relapsed had com plete hypophysectomies

DR MATSON Dr Nickson did your patients all die of neo plasm and not of radiation?

DR LIPSETT I think we have to say that at least two patients and possibly three had radiation damage Two patients died re cently of radiation damage All three patients had active disease but you would not have expected them to die of this amount of disease They all had clinical evidence of extensive central nervous system damage at the time they died

DR ADAIR If you cut down the size of the betatron portal, what do you think the effect might be?

DR NICKSON Dr Adair it is perfectly possible particularly with the betatron with the 3 by 3 cm port to have quite reason able distribution of energy although you do have fall off toward the edges which is another reason for the larger field I would still feel that we probably would have damage and with any photon beam *I don t see how you are going to protect the optic nerve* You have spreading out so you are going to catch the optic nerve with the charged particle beam

DR BAKER No bone marrow effect no depression?

DR NICKSON Nothing that we saw

DR RAY There was one quite interesting case although it is not entirely pertinent A man with acromegaly who had had one series of conventional x ray treatment and then received betatron therapy subsequently developed signs of a brain tumor in the

right temporal lobe he had clinical signs of increased intracranial pressure and shift of the pineal At operation I took this immediately to be a glioblastoma It had all the appearance of degenerating glioma but it proved to be a radiation effect We have another acromegalic who received unwittingly I believe 10 000 r with a standard machine and he developed signs of a brain tumor in the left frontal lobe which we operated on It had the same appearance These effects have been reported by Arnold and Bailey [8] and others in the high voltage treatment of brain tumors It simply supports what Dr Nickson said that the effects on the adjacent tissues have to be taken into consideration It is too bad we don t have Dr John Lawrence here to talk about his more controlled beam but even with his methods he cannot avoid the hypothalamus and optic nerve

CHAIRMAN PEARSON Dr Lawrence was unable to come His associate visited me recently and we discussed their results which are still preliminary They are using a deuteron beam They have taken great pains with the rotational technique to try to avoid damage to the tissues outside the sella turcica There is some evidence of decreased pituitary function in their patients as measured by gonadotrophin excretion and measurements of thyroid function without signs of serious neurological damage as yet

CHAIRMAN PEARSON One of the subjects studied by Dr Woolley was particularly interesting She had been castrated for carcinoma of the breast and three months afterward developed a classical Cushing s syndrome She was too sick to operate on and that is the reason we went ahead with the betatron radiation I suppose this might have some bearing too on the histopathology here

DR WOOLLEY The histopathology is very difficult to interpret on a physiological basis i e between storage phenomena or excess secretion phenomena

DR MATSON Why do you think she had the Cushing s syndrome?

CHAIRMAN PEARSON At post mortem the adrenals were hyperplastic not adrenal carcinoma or adenoma and we assumed that it must have been stimulation from the pituitary

DR LIPSETT Hyperplastic with small adenomas as well

DR. BAKER You did not find prickle cells?

DR WOOLLEY I did not see them

DR. MATSON The radiation did not affect it?

CHAIRMAN PEARSON No it did not affect it.

DR BAKER Dr Woolley have you seen any of the cells that Dr Grace Field had the hypertrophic amphophils?

DR WOOLLEY I believe her amphophils are somewhat related to my delta cells

DR BAKER These universally disappear when you give corti sone thyroid or estrogen or testosterone

DR WOOLLEY She accuses these as being perhaps also ACTH producing cells

DR ADAIR And gonadotrophin

DR BAKER These disappear with the institution of hormones

DR WOOLLEY We have got too many hormones to assign one to each cell type

DR BAKER Isn t it possible that one cell could make a multiple number of hormones? Certainly any cell makes a number of anti bodies It is possible that a cell can make a number of hormones I don t think it is at all unreasonable

DR KENNEDY Is electron microscope work being done on any of the pituitaries being removed?

CHAIRMAN PEARSON I don t believe so

DR WOOLLEY There is as you well know a distribution of cells within the pituitary which really should be differentially counted Satisfactory counts could not be obtained with the pitui tary fragments at hand

DR KENNEDY It seems that all the pituitary tissues that are being removed ought to be utilized more extensively because the pathology of the pituitary is all based on post mortem data To be able to do some work with fresh tissue in staining would answer a lot of questions of what type of cells are present At the result of this particular meeting perhaps some accumulation of data re- garding the pituitary tissues should be worthwhile considering

DR RAWSON Are you convinced that Sommer s report [9] on the increased amphophils in his patients is reliable?

DR BAKER I don t think we have enough evidence to support that Most of our patients have been treated with hormones for some time prior to removal of the pituitary We have very few untreated carcinomas of the breast I went over all the material before I came down here The few that have been untreated do show a large proportion of these hypertrophic amphophil cells

I think it would be wise if we followed Dr Kennedy's suggestion and made pituitary tissue available to pathologists for study

DR RAWSON Another thing that would be desirable would be to assay as many of these pituitaries as possible for growth hormone

DR LUFT We have done that We have been sending our pituitaries to the University of California for several years now Dr C H Li has assayed them He has informed me that he gets rather high figures of growth hormone from cancer patients

CHAIRMAN PEARSON We have twenty minutes left to finish our discussion of any aspects of our conference Now is the time to raise any last minute questions I would be delighted for anybody to do so

DR EVANS May I raise a question which can probably be quickly disposed of? I am concerned about the variations in tumor type Is this an important factor or not? Is the condition of the host far more important than the particular variant of the tumor type?

CHAIRMAN PEARSON I think you are referring to the question of whether or not there is one type of breast carcinoma that will respond to alterations of endocrine environment I can state very briefly our concept about it at the moment and I am sure there are other opinions here Our general concept as the result of observations of removal of endocrine organs is that there is a type of tumor that is dependent upon the hormone environment, particularly upon estrogen and possibly upon pituitary hormones There are some tumors that seem to be completely uninfluenced by alteration of endocrine environment We have tried to correlate response to endocrine therapy with pathologic characteristics of the tumor tissue and with any clinical features of the disease to see if we could find differences between the tumor type that is dependent upon hormones and the type that is not but we have been completely unable to categorize these patients in any way either from the pathology or from the clinical course of their disease We just do not know why one tumor is dependent upon hormonal environment and another that looks exactly the same is apparently completely uninfluenced We have wondered about the possibility that the tumor and the patient may undergo many adaptations in the natural history of the disease perhaps early in the course of the disease more tumors possibly all of them are dependent upon

hormones Our data do not suggest this On the other hand we have not done much in the way of ablative therapy in patients with early tumors I am sure there are other opinions about this

DR ADAIR How do you account for the fact that Dr Huggins [30] with all his experience of over 200 cases thinks there is but one type which responds—the adenocarcinoma? And this group of observers here present, disagrees with that viewpoint?

DR FORREST The top pathologists in Glasgow have a consider able experience in breast cancer They do not agree with Huggins classification

DR LIPSETT Dr Frank Foote of our pathology group does not agree and finds it very difficult to classify any tumor using Dr Huggins classification

DR ADAIR There is one thing which I consider to be impor tant, namely the test of hormone therapy We have had the ex perience of obtaining striking improvement following adrenalec tomy in cases *not* of the adenocarcinoma type but which had a good previous regression with testosterone therapy

DR TAYLOR We tried to make a similar correlation in our pa tients who were adrenalectomized We examined surgical speci ments in eighteen primary untreated tumors Slides taken from one portion of the tumor appeared completely different from those of tissue from another area This so completely confused us that we could not really classify any of the breast tumor cases

DR ADAIR It is very much like the classification for the grading of tumors You find Grade II in one spot and Grade IV in another area

DR. TAYLOR We could not get any real correlation There is a tendency if the tumor is mainly differentiated that it is a better responder but I certainly cannot pick it out and say this patient will respond and this one won t

DR JESSIMAN It is important to accentuate the fact that there is more than one histological type of tumor in a carcinoma of the breast If one searches hard enough one may find several differ ent types of histology in the same breast I would like to reinforce something Dr Pearson said about the hormone sensitivity of tu mors We certainly found with our stimulation tests some of these tumors in their life history lose their sensitivity or their ability to be stimulated by hormones In other words if you give them a stimu lation test now they may give a positive response and in a year

and one half's time they will give a negative response They appear to have gone into autonomous phase and we feel that then possibly they are beyond any effective treatment by hormone ablation surgery

Dr Kennedy I think too many people pay attention to cells and not enough to the stroma In the estrogen treated patients the slow growing low degree malignancy tends to respond more frequently than the high degree malignancy Despite this sort of trend some of the best responses were Grade IV malignancy So I don t think there is any possible way that you could select from the pathological picture what patient will or will not respond

Dr Matson Has anyone carried out any systematic stimulation and inhibition tests on soft tissue metastases with biopsy studies? In other words in the Grade III type of case you were speaking about last night say with supraclavicular metastases but no bone or other distant lesions of any kind giving such a patient estrogen stimulation with pre and post biopsies or cortisone inhibition with pre and post biopsies to see if there is any possibility of learning whether you would be justified in going ahead with ablative treatment immediately at that phase?

Chairman Pearson We have not done this I think the closest approximation to this were some studies that Dr Sullivan of our chemotherapy group did with skin metastases In patients he injected estrogen androgen and cortisone locally into the tumor to see whether or not he could demonstrate growth or inhibition He took small punch biopsies before and after the injection He felt that this might prove to be a useful way of selecting patients Of course not all patients have lesions on the surface that you can do this with It also raised the question of whether or not you could take a sample of the tumor at operation grow it in a guinea pig rat or hamster and see if you could stimulate it with hormones It has turned out that breast cancer is one of the most difficult tumors to try to grow in the animal Our group here has tried it in x ray treated rats and cortisone treated rats and have not been able to get these tumors to grow They can get survival of cells and they have seen slight changes with hormones but not enough to draw any hard and fast conclusions about

Dr Baker A number of years ago in 1950 we tried to approach the subject using amino acid incorporation in the malignant cells Unfortunately we could not separate the stroma from

the cells There are now some newer techniques to separate stroma from cells and I think we are going to reinvestigate this aspect of it to see whether or not we can by biochemical tests see if there is a difference in the incorporation Another comment I would like to make is that once again we neglect the host We have not been able to define by pathological type the tumor that responds to estrogen therapy but just from the clinical observation it appears to be the shriveled up elderly looking woman who seems to be de pleted of all hormones who is able to respond Take the young looking woman who appears ten or fifteen years younger than she is that is the type of woman who does not respond Once again it means that we should study the host The host is really the major criterion

DR ADAIR When we were with our consultants before the Therapy Committee in Washington we set up the problem at that time to see if our pathologic consultants Dr Ackerman Dr Stout and Dr Stewart could distinguish in a series of skin nodules which were pre treatment and which were post treatment That study brought out the fact that there appeared to be no pathologic char acteristics that distinguished the pre and post treatment nodules I seems to me that we have so many things in common in our at tacks on the overall problem the one tumor that is treated by estrogen the one treated by oophorectomy the one treated by the ablation of the hypophysis look all the same It may be by at tacking the major gland we are going to get further and hold our gain much longer I certainly hope so Is that the concensus here?

DR BERGENSTAL That is what I wondered this morning I have been asking Dr Luft and the others about the length of remission that we are getting and I think that certainly the feel ing of Dr Luft who has had the longest opportunity for follow up is that it is approximately two years From adrenalectomy we can obtain at best twelve months and oophorectomy may give six to nine months So it looks like we are going to get a longer re mission period from hypophysectomy which is so important if we are going to continue to use this procedure

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